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Review article

How cardiomyocyte excitation, calcium release and contraction become altered with age

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ABSTRACT

Cardiovascular disease is the main cause of death globally, accounting for over 17 million deaths each year. As the incidence of cardiovascular disease rises markedly with age, the overall risk of cardiovascular disease is expected to increase dramatically with the aging of the population such that by 2030 it could account for over 23 million deaths per year. It is therefore vitally important to understand how the heart remodels in response to normal aging for at least two reasons: i) to understand why the aged heart is increasingly susceptible to disease; and ii) since it may be possible to modify treatment of disease in older adults if the underlying substrate upon which the disease first develops is fully understood. It is well known that age modulates cardiac function at the level of the individual cardiomyocyte. Generally, in males, aging reduces cell shortening, which is associated with a decrease in the amplitude of the systolic Ca^{2+} transient. This may arise due to a decrease in peak L-type Ca^{2+} current. Sarcoplasmic reticulum (SR) Ca^{2+} load appears to be maintained during normal aging but evidence suggests that SR function is disrupted, such that the rate of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA)-mediated Ca^{2+} removal is reduced and the properties of SR Ca^{2+} release in terms of Ca^{2+} sparks are altered. Interestingly, Ca^{2+} handling is modulated by age to a lesser degree in females. Here we review how cellular contraction is altered as a result of the aging process by considering expression levels and functional properties of key proteins involved in controlling intracellular Ca^{2+}. We consider how changes in both electrical properties and intracellular Ca^{2+} handling may interact to modulate cardiomyocyte contraction. We also reflect on why cardiovascular risk may differ between the sexes by highlighting sex-specific variation in the age-associated remodeling process. This article is part of a Special Issue entitled CV Aging.

Contents

Abbreviations: AP, action potential; APD_{50}, AP duration at 50% repolarization; APD_{90}, AP duration at 90% repolarization; I_{KATP}, ATP-sensitive K^+ current; CaMKII, Ca^{2+}-calmodulin-dependent kinase II; DHP receptors, 1,4-dihydropyridine receptors; EC-coupling, excitation–contraction coupling; HFpEF, heart failure with preserved ejection fraction; I_{K1}, inward rectifier K^+ current; $I_{Ca\text{-}L}$, L-type Ca^{2+} current; MHC, myosin heavy chain; PLB, phospholamban; PKA, protein kinase A; RMP, resting membrane potential; RyRs, ryanodine receptors; SR, sarcoplasmic reticulum; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase; I_{Ks}, slow delayed rectifier K^+ current; NCX, Na^+/Ca^{2+} exchanger; I_{TO}, transient outward current

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1. Introduction

The incidence of cardiovascular disease rises dramatically with age. This may not be surprising, as the aging process itself leads to important structural and functional remodeling of the heart. There is growing evidence that this myocardial remodeling can modify contractile function in the aging heart, even in the absence of overt systemic cardiovascular disease. For example, the ability to augment contractile force in response to stimuli that increase demand, such as exercise, declines with age and relaxation is compromised. These changes arise, in part, from the structural remodeling and hypertrophy that accompany the aging process, although age-associated changes in contractile function also reflect underlying modifications at the level of the individual ventricular myocyte.

Contractile dysfunction arises as a consequence of disruption in the sequence of events that link cardiomyocyte excitation to intracellular Ca^{2+} release and contraction, a process known as excitation–contraction (EC)-coupling. Recent evidence suggests that the influence of age on cardiac EC-coupling differs markedly between the sexes. Understanding how age influences the EC-coupling pathway at the cellular level in both males and females can help us understand why men and women are susceptible to different cardiovascular diseases as they age and may help develop strategies for the prevention and treatment of cardiovascular disease in this vulnerable population. This review explores the influence of age on fundamental cardiomyocyte function, including myocyte excitation, intracellular Ca^{2+} release and cell shortening, as well as age-dependent changes in the ion channels and Ca^{2+} handling proteins responsible for these cellular events.

2. Impact of age on cardiac contractile function

Clinical studies in healthy individuals have established that aging is associated with marked changes in cardiac structure, such as left ventricular hypertrophy and remodeling of the extracellular matrix [1]. Advanced age is also characterized by modifications in cardiac function [1]. Studies of myocardial function in healthy individuals at rest have shown that cardiac output and myocardial contractility are not affected by age [2–6]. By contrast, the ability to augment contractile function when demand is high during activities such as exercise is compromised in older adults when compared to younger individuals [1,5,6]. Aged individuals also have slower contractions and less complete relaxation when compared to younger people, which suggests that diastolic function declines with age [1,6,7]. Interestingly, there is evidence that myocardial contractility is better preserved in older women when compared to age-matched men [8]. This observation suggests that there may be male–female differences in the effect of age on myocardial contractile function.

2.1. Myocardial contractile function in aging animal models

Various animals have been used to investigate the age-dependent changes in contractile function seen clinically. Rats and mice exhibit a 50% mortality rate at approximately 24 months of age [9], which is comparable to the 50% mortality rate seen in 85-year-old humans [10]. Therefore, most studies use mice or rats that are approximately 24 months of age as models of human aging and the literature reviewed here focuses on rodents that are at least 18 months of age. Structural changes similar to those seen in older humans, including left ventricular hypertrophy and extracellular matrix remodeling, have been demonstrated in aged mice [11]. While the impact of age on cardiac contractile function at rest and during exercise has not yet been investigated in conscious rodents, in vivo echocardiography studies in anesthetized animals show that age reduces fractional shortening and ejection fraction [12–14]. These studies also demonstrate differences in myocardial relaxation in aged rodents, which indicates that diastolic function deteriorates with age [13,15]. Whether age-dependent cardiac dysfunction differs between the sexes in rodents as it does in humans is unclear, as these studies used males only [12,13] or the sex of the animal was not specified [14,15].

The influence of age on cardiac contractile function also has been explored in intact heart models. Studies in Langendorff-perfused hearts show that left ventricular end-diastolic pressure rises with age while peak developed pressure declines, which suggests that aged animals develop both systolic and diastolic dysfunction [15]. Furthermore, peak tension development is reduced with age [16], especially at higher heart rates [17]. Other studies showed that the maximum rate of tension development ($+dT/dt$) and maximum rate of relaxation ($-dT/dt$) are slowed with age [16,17]. Using isolated cardiac muscle preparations, some studies report that there is no age-related decline in peak tension in isolated papillary muscles or trabeculae [18,19], while others report a reduction with age [20]. On the other hand, there is general agreement that contraction duration is prolonged with age, with an increase in both time-to-peak tension and half-relaxation time [18–22]. Thus, evidence from studies *in vivo*, in intact hearts and in cardiac muscles demonstrates that contractions are smaller and slower in the aging heart. On the other hand, whether this differs between the sexes is unclear, as these studies used male animals only [16,18–22] or did not specify the sex of the animal [15,17]. Together, these observations indicate that cardiac contractile function declines with age, at least in male animals.

2.2. Cellular contractile dysfunction in aged male animals

As contractions are initiated by a transient rise in Ca^{2+} in cardiac myocytes, age-dependent changes in cardiac contractile function may reflect disruptions in EC-coupling at the cellular level [23,24]. During the action potential (AP), Ca^{2+} enters the cell through L-type Ca^{2+}

channels that open in response to depolarization. This small influx of Ca^{2+} triggers ryanodine receptors (RyRs) to open, allowing release of a larger amount of stored Ca^{2+} from the sarcoplasmic reticulum (SR). SR Ca^{2+} is released in the form of discrete, subcellular units called Ca^{2+} sparks that fuse to form the Ca^{2+} transient [25]. Ca^{2+} then binds to myofilaments to initiate contraction. Relaxation occurs mainly by Ca^{2+} being sequestered by the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), whose activity is modulated by its endogenous inhibitor, phospholamban (PLB). Ca^{2+} is also removed from the cell, chiefly by the Na^{+}/Ca^{2+} exchanger (NCX) operating in its forward-mode although it also can operate in the reverse direction, bringing Ca^{2+} into the cell in exchange for Na^{+} [26]. Contractile dysfunction in the aging heart may arise, in part, because the ability of individual myocytes to contract is adversely affected by the aging process.

A number of studies have investigated the impact of age on cardiac contraction by comparing the amplitudes and time courses of contractions, measured as unloaded cell shortening, in ventricular myocytes isolated from young adult (2–7 months of age) and aged (20–33 months of age) male rats and mice (Table 1). It is well known that the aging process leads to a marked increase in the size of ventricular myocytes through an increase in cardiomyocyte length, width and area (Supplemental Table 1). This likely contributes to the age-dependent hypertrophy seen in intact hearts [11]. Because of this age-associated cellular hypertrophy, contractions are typically normalized to cell length in functional studies. With this approach, there is now convincing evidence that peak cell shortening declines with age in male mice ([12,15,27–31] but *c.f.* [32,33]) and guinea pigs [34]. Many studies also have shown similar effects in male rats [35–39], although others report peak contraction to be unaltered during aging [40–47]. Interestingly, all studies in rats and mice that showed a decline in peak contraction with age used rapid pacing frequencies (*e.g.* between 1 and 9 Hz), while those reporting no effect typically paced cells at slow rates (*e.g.* $\leq$ 0.5 Hz), well below physiological for rodents [48]. This suggests that it is important to use cells that are challenged with physiological or near-physiological pacing frequencies when investigating the impact of age on cell shortening. These observations support the conclusion that a decline in the ability of individual cardiomyocytes to contract contributes to the age-dependent reduction in myocardial contractility seen in intact hearts, at least in male animals when cells are paced at physiological rates.

To determine whether the age-dependent slowing of contraction seen in multicellular preparations arises from slower contractions at the level of the cardiomyocyte, time-to-peak contraction and relaxation rates have been quantified, as summarized in Table 1. Time-to-peak contraction is prolonged with age in many studies in male animals [15,28,31,32,34,35,42,46], although some have found no age-dependent change [12,36,43–46] or even a decrease [33]. Interestingly, most of these latter studies [12,43–46] used sub-physiological pacing rates (*e.g.* 0.1–0.5 Hz), which may mask age-dependent slowing of contraction that is seen at faster rates. There also is considerable evidence that relaxation rates are slowed with age in cells from male rats, mice and guinea pigs, regardless of pacing frequency [12,15,29–32,34,35,37,38,43–45], though some do report no age-dependent slowing [27,28,33,36,42,46,47]. Taken together, these observations suggest that cardiomyocyte contractions are smaller and slower in cells from aged males when compared to younger adults. These data from unloaded cardiomyocytes are similar to data from multicellular preparations subjected to preload, as discussed in Section 2.1. This suggests that age-dependent changes in contraction are independent of preload, although additional investigation will be required to confirm this experimentally.

Table 1
Impact of age on cardiomyocyte contraction.

Sex	Component	Functional change[a]	Species	References[b]
Male	Peak contraction	↓	Rat	[35–39]
			Mouse	[12,15,27–31]
			Guinea pig	[34]
		↔	Rat	[40–47]
			Mouse	[32,33]
	Time-to-peak contraction	↑	Rat	[35,42,46]
			Mouse	[15,28,31,32]
			Guinea pig	[34]
		↔	Rat	[36,43–45,47]
			Mouse	[12]
		↓	Mouse	[33]
	Relaxation rate	Slowed	Rat	[35,37,38,43–45]
			Mouse	[12,15,29–32]
			Guinea pig	[34]
		↔	Rat	[36,42,46,47]
			Mouse	[27,28,33]
Female	Peak contraction	↔	Rat	[36,49–51]
			Mouse	[28,33]
	Time-to-peak contraction	↔	Rat	[36]
			Mouse	[28]
		↓	Mouse	[33]
		↑	Rat	[49,51]
	Relaxation rate	↔	Rat	[36]
			Mouse	[28,33]
		Slowed	Rat	[49,51]

[a] Values are expressed relative to young adults (2–7 months of age for rats and mice; 1–3 months for Guinea pigs); aged rats and mice were between 20–33 months of age and older Guinea pigs were 13–16 months.
[b] In some studies [15,38,39,43,45], the sex of the animals was not specified and is assumed to be male.

2.3. Contractions in myocytes from aged females

Most experimental studies of the aging heart have used male animals, presumably under the assumption that results obtained in older males can be extrapolated to females. However, there is emerging evidence that the aging process affects cardiac function rather differently in the two sexes. Although information is limited, a few studies have evaluated contractile function in ventricular myocytes from females (Table 1). Whether contractions are slowed with age in females is controversial, but it is clear that peak contractions do not decline [28,33,36,49–51]. Even when cells are stimulated at relatively rapid rates (*e.g.* 2–4 Hz), peak contractions are not affected by age in females [28,36,50]. As most studies in males report a marked reduction in contraction amplitudes with age (Table 1), these observations suggest that the aging process has distinct effects on male and female hearts. Certainly, these data suggest that it is essential to consider both male and female animals in experimental studies of the aging heart.

2.4. Contractile proteins in the aging heart

Modifications in contractile function could be mediated by effects of age on contractile proteins. To investigate this, a number of investigators have compared myofilament proteins in young adult and aged hearts. The results of these studies are summarized in Supplemental Table 2. There is compelling evidence for an age-related shift from the fast α myosin heavy chain (MHC) isoform to the slower β isoform in hearts from both sexes ([51–55] but *c.f.* [49]). Phosphorylation of troponin I also declines with age in males and females [46,49,54]. The predominance of the slower β-MHC isoform coupled with reduced phosphorylation of troponin I could account for the slowing of relaxation reported in many studies of the aging heart (Table 1). Other investigations have demonstrated an age-associated reduction in myofilament Ca^{2+} ATPase activity in male hearts [20,32,52], which is compatible with the prolonged time-to-peak contraction seen in the aging male heart (Table 1). Whether myofilament Ca^{2+} ATPase activity also decreases with age in hearts from females has not yet been investigated.

Table 2
Age-dependent changes in cardiomyocyte calcium transients.

Sex	Component	Functional change[a]	Species	References[b]
Male	Peak Ca^{2+} transient	↓	Rat	[36,39]
			Mouse	[12,15,28–30]
		↔	Rat	[40,41,45]
			Mouse	[27,31]
		↑	Mouse	[32]
	Time-to-peak Ca^{2+} transient	Prolonged	Rat	[39,45]
			Mouse	[28,68]
		↔	Rat	[36,47]
			Mouse	[31–33]
	Ca^{2+} transient decay rate	Slower	Rat	[36,39,45]
			Mouse	[12,15,27,30–32,68]
		↔	Rat	[47]
			Mouse	[33]
	Diastolic Ca^{2+}	↑	Rat	[45,47]
			Mouse	[15,68]
		↔	Rat	[36]
			Mouse	[12,33,103]
		↓	Mouse	[28]
Female	Peak Ca^{2+} transient	↔	Rat	[36,49–51]
			Mouse	[28]
			Rabbit	[70]
		↑	Sheep	[71]
	Time-to-peak Ca^{2+} transient	↔	Rat	[36]
			Mouse	[28,33]
		Prolonged	Rat	[51]
			Sheep	[71]
	Ca^{2+} transient decay rate	↔	Rat	[36]
			Mouse	[28]
			Rabbit	[70]
		Slower	Rat	[49,51]
		Faster	Mouse	[33]
			Sheep	[71]
	Diastolic Ca^{2+}	↔	Rat	[36]
			Mouse	[28,33]
			Sheep	[71]

[a] Values are expressed relative to young adults (2–7 months of age for rats and mice; 5–9 months for rabbits; 18 months for sheep); aged rats and mice were between 20–33 months of age, aged rabbits were 48–72 months and older sheep were >96 months.
[b] In some studies [15,39,45,68], the sex of the animals was not specified and is assumed to be male.

3. Ca^{2+} homeostasis in ventricular myocytes from aged animals

As discussed in Section 2.2, contractions are initiated by an increase in intracellular Ca^{2+} levels in individual myocytes. These Ca^{2+} handling processes are tightly controlled in the young adult heart and are regulated by phosphorylation through the cAMP/protein kinase A (PKA) and Ca^{2+}-calmodulin-dependent kinase II (CaMKII) pathways [56,57]. Careful control of Ca^{2+} in the cardiomyocyte is crucial, as intracellular Ca^{2+} is required to initiate contraction but disruption of Ca^{2+} handling contributes to cardiovascular diseases [58] and may predispose the aging heart towards the development of these diseases [59].

3.1. Influence of age on Ca^{2+} homeostasis in ventricular myocytes from male animals

To determine whether age-related disruptions in cardiac contractions are accompanied by parallel changes in underlying Ca^{2+} transients, the impact of age on Ca^{2+} homeostasis in ventricular myocytes has been investigated. The results of these studies are summarized in Table 2. There is a growing consensus that peak Ca^{2+} transients decline with age in male rodents [12,15,28–30,36,39], although some report no age-dependent change [27,31,40,41,45] and one study even found an increase with age [32]. As with contractions, smaller Ca^{2+} transients in aged myocytes are typically observed in studies that challenge cells with rapid pacing rates [12,15,28–30,36,39], while those that report no effect tend to use lower stimulation rates [27,40,41,45]. Thus, like the inability of the aged human heart to augment contractile function during exercise (as discussed in Section 2), aged cardiomyocytes appear less able to respond to higher rates of stimulation and thus the aged phenotype may be unmasked at increased rate.

Since increasing rate revealed age-associated changes in contraction and intracellular Ca^{2+}, the effects of age observed at faster pacing rates may be Ca^{2+}-dependant, at least in rodents. It is well known that CaMKII plays an important role in the response to increased stimulation rate by phosphorylating key Ca^{2+} handling proteins (*e.g.* [60–64]). It is therefore interesting that levels of CaMKII (δ-isoform) are reduced in the aged male rat heart and that CaMKII-mediated phosphorylation of key Ca^{2+} handling proteins (RyR, SERCA and PLB) also is reduced [65]. Thus, we might speculate that, at least in the male rat, a decrease in CaMKII phosphorylation results in the aged heart being less able to respond to increases in rate. Whether age influences CaMKII levels in females is not yet known, although sex differences in CaMKII activation have been reported in hearts from younger animals [66]. Although age affects contractions and Ca^{2+} transients primarily at rapid pacing rates in male rodents, whether similar frequency-response results would be obtained in larger mammals is not clear. Few aging studies have examined larger mammals (*e.g.* sheep, rabbits) and those that have used female animals, where age-dependent changes are minimal. There may be important differences in frequency-responses between rodents and larger mammals, as rodents have much less contractile reserve than larger species [67].

There is also good evidence that the time course of Ca^{2+} release is prolonged with age in males, with many reporting an increase in time-to-peak transient ([28,39,45,68] but *c.f.* [31–33,36,47]) and virtually all reporting a marked prolongation of Ca^{2+} transient decay with age ([12,15,27,30–32,36,39,45,68] but *c.f.* [33,47]). One might predict that slowed decay would lead to an increase in diastolic Ca^{2+} levels with age in cells from male animals. Still, there is no clear consensus on whether diastolic Ca^{2+} levels are affected by age, as there is evidence for unchanged, increased and reduced levels in cells from aged males (Table 2). Disparate results could be due to differences in experimental conditions between studies. Interestingly, under some circumstances slower Ca^{2+} transients can actually augment contraction, as myofilaments are exposed to Ca^{2+} for a longer period of time [69]. It is possible that this effect might mask an even larger decrease in myofilament function in aged cardiomyocytes, although additional experiments will be required to test this experimentally. While slowed decay is consistent with reduced CaMKII phosphorylation of SERCA/PLB, altered protein levels also appear to be important in defining this slow decay and are discussed in Section 5.1. Taken together, these findings suggest that smaller peak contractions which relax more slowly are attributable, at least in part, to smaller Ca^{2+} transients that decay more slowly in myocytes from males.

3.2. Ca^{2+} homeostasis in myocytes from aged females

Table 2 also summarizes results of several studies that have investigated the impact of age on Ca^{2+} transients in cells from females. Unlike males, peak Ca^{2+} transients are not affected by age in cardiomyocytes from female rats, mice or rabbits [28,36,49–51,70] and Ca^{2+} transients actually increase with age in female sheep [71]. This is true even when myocytes are paced between 2 and 4 Hz [28,36]. While most studies have found that time-to-peak transient and Ca^{2+} transient decay rates are not affected by age in females ([28,36,70] but *c.f.* [33]), some report that time-to-peak is prolonged and decay rates are slower in cells from aged animals [49,51]. Interestingly, Ca^{2+} transient decay rates actually increase with age in the sheep model [71]. Consistent with these results, diastolic Ca^{2+} levels are not affected by age in myocytes from female animals (Table 2). These studies indicate that age has relatively little effect on Ca^{2+} transient amplitude in cardiomyocytes from female animals, which differs markedly from observations in males. Still, additional studies that explore rapid pacing rates in female myocytes could be informative. It is also important to note that cardiomyocyte contractions

and Ca^{2+} transients differ between the sexes in cells from young adult animals, with young adult females typically having smaller and slower contractions and Ca^{2+} transients than age-matched males [72,73]. Thus, contractions and Ca^{2+} transients in myocytes from aged males become similar to responses in females, regardless of age.

4. The influence of age on cardiac excitation

Ca^{2+} release from the SR is initiated by the cardiac AP, which arises as a result of changes in permeability of the sarcolemma to Na^+, Ca^{2+} and K^+. Therefore, the effect of age on cardiac APs and underlying ionic currents has been explored by a number of investigators.

4.1. RMP and AP configuration in myocytes from aged animals

Table 3 summarizes the age-dependent changes in resting membrane potential (RMP) and AP configuration in studies of intact ventricular muscle and isolated ventricular myocytes. Most studies used adult (1–6 months of age) and aged (18–31 months of age) male rats. As shown in Table 3, there is very little evidence that age influences RMP ([18,19,40,74–79] but *c.f.* [47,81,82]). Most studies also report that age has no effect on the amplitude of the cardiac AP ([74,75,77,79–81] but *c.f.* [76,78,82]). By contrast, there is general agreement that age causes a prolongation in AP duration at 50% repolarization (APD_{50}) ([18,38, 74–77,79,81] but *c.f.* [40,78,82]). Furthermore, virtually all investigations report an age-associated increase in AP duration at 90% repolarization (APD_{90}) in ventricular myocyte and tissues from male rats ([19,38, 74,76–78,80–82] but *c.f.* [40]). A similar pattern is seen in ventricular myocytes from aged female sheep [71] but not rabbits [70]. Still, one cannot directly compare APs in larger mammals such as rabbits and sheep with those in rats, as different K^+ currents are responsible for repolarization [83]. More studies are needed to determine whether age has similar effects on cardiac excitation in males and females. This is important, as there is evidence for male–female differences in APD in ventricular myocytes from young adult animals [73]. Whether such alterations persist in aging is important, as men and women are susceptible to different types of arrhythmias at all ages [84,85].

The shape of the cardiac AP is inextricably linked to Ca^{2+} handling in the heart. When myocytes from aged rats were stimulated with a short 'young type' AP, instead of their native long AP, Ca^{2+} transient amplitude decreased while peak $I_{Ca\text{-}L}$ increased, prompting the authors to suggest that old rats utilize AP prolongation to sustain youthful Ca^{2+} regulation [86]. In a separate study in rats where intracellular Ca^{2+} was buffered with EGTA, AP prolongation was greater in young vs. aged myocytes and resulted in a loss of the age-associated increase in APD suggesting that a Ca^{2+}-dependent process plays a part in AP prolongation in aging [79]. Under these circumstances, age-related changes in APD appear to potentiate the Ca^{2+} transient, which may itself act to potentiate APD. This may not be the case for larger mammals, where an increase in APD can attenuate SR Ca^{2+} release [87,88]. Prolongation of the action potential also may help explain the age-related slowing of the rising phase of the Ca^{2+} transient, as increased APD is known to de-synchronize SR Ca^{2+} release [88]. Additional confocal microscopy and imaging experiments to investigate whether aging leads to de-synchrony of SR Ca^{2+} release would be of interest. Age-dependent changes in $I_{Ca\text{-}L}$ also may influence Ca^{2+} release, as discussed in Section 4.2.

Table 3
Impact of age on cardiac resting and action potentials.

Sex	Component	Functional change[a]	Species	Reference[b]
Male	RMP	↔	Rat	[18,19,40,74–79]
		↓	Rat	[47]
		↑	Rat	[81,82]
	AP amplitude	↔	Rat	[74,75,77,79–81]
		↑	Rat	[76,78,82]
	APD_{50}	↑	Rat	[18,38,74–77,79,81]
		↔	Rat	[40,78,82]
	APD_{90}	↑	Rat	[19,38,74,76–78,80–82]
		↔	Rat	[40]
Female	RMP	↔	Sheep	[71]
	AP amplitude	↔	Sheep	[71]
	APD_{90}	↔	Rabbit	[70]
		↑	Sheep	[71]

[a] Values are expressed relative to young adults (1–8 months of age for rats; 18 months for sheep); aged rats were between 18–31 months of age and older sheep were >96 months.
[b] In the study by Weisser-Thomas et al. [38] the sex of the animals was not specified and is assumed to be male.

4.2. Age-associated modifications in $I_{Ca\text{-}L}$ in ventricular myocytes

Prolongation of the AP in aging could arise from changes in ionic currents that either prolong depolarization or attenuate repolarization. Whether Na^+ currents are influenced by age in ventricular myocytes has not yet been investigated. On the other hand, many studies have focussed the effect of age on Ca^{2+} influx via L-type Ca^{2+} channels, as this depolarizing current is the primary trigger for SR Ca^{2+} release in the heart. Whether the density of L-type Ca^{2+} channels is affected by age has been investigated by quantifying either the density of 1,4-dihydropyridine (DHP) receptors or the expression of L-channel protein in hearts from male rodents (Table 4). These studies clearly show that L-type Ca^{2+} channel density and expression does not change with age ([31,32,45,89,90] but *c.f.* [91]). Others have looked for evidence of age-related modifications in the amplitude and characteristics of $I_{Ca\text{-}L}$. In these studies, transmembrane currents are normalized to cell capacitance to compensate for the age-related increase in cell membrane area consistently seen in ventricular myocytes (Supplemental Table 1).

Table 4
Influence of age on sarcolemmal proteins and currents.

Sex	Component	Functional change[a]	Species	Reference[b]
Male	L-channel	↔ DHP receptor density	Rat	[45,89]
			Mouse	[31,32]
		↓ DHP receptor density	Hamster	[91]
		↔ protein	Rabbit	[90]
	$I_{Ca\text{-}L}$	↓ peak $I_{Ca\text{-}L}$	Rat	[36,78]
			Mouse	[28]
			Rabbit	[90]
		↔ peak $I_{Ca\text{-}L}$	Rat	[47,79]
		Slowed inactivation	Rat	[78,79]
			Mouse	[28]
	K^+ currents	↔ I_{TO}	Rat	[75]
		↓ I_{TO}, I_{KATP}	Rat	[79,81,95]
		↑ I_{TO}, I_{K1}	Rat	[78,79]
	NCX	↔ NCX mRNA	Mouse	[32]
		↔ NCX protein	Rat	[44,82,99]
			Mouse	[12,31]
			Rabbit	[90]
		↔ NCX activity	Rat	[80]
		↓ NCX protein	Rat	[43,45,100]
			Mouse	[17]
		↓ NCX activity	Rat	[101,102]
		↑ forward mode current	Rat	[82]
Female	L-Channel	↔ L-channel protein	Rabbit	[70]
	$I_{Ca\text{-}L}$	↓ peak $I_{Ca\text{-}L}$	Rat	[36]
		↔ peak $I_{Ca\text{-}L}$	Mouse	[28]
			Rabbit	[70]
			Rat	[94]
		↑ peak $I_{Ca\text{-}L}$	Sheep	[71]
		↔ inactivation	Mouse	[28]
	K^+ currents	↔ I_{TO}, I_{K1}, I_{Ks}	Rabbit	[70]
	NCX	↔ NCX protein	Rabbit	[70]
		↔ forward mode current	Sheep	[71]

[a] Values are expressed relative to young adults (2–7 months of age for rats and mice; 6 months for rabbits; 4 months for hamsters; 18 months for sheep); aged rats and mice were between 20–31 months of age, aged rabbits were 26 months, aged hamsters were 20 months and older sheep were >96 months.
[b] In some studies [17,43,45], the sex of the animals was not specified and is assumed to be male.

While a few investigations report no age-dependent change [47,79], most have found that peak $I_{Ca\text{-}L}$ declines with age [28,36,78,90] and all studies report that $I_{Ca\text{-}L}$ inactivation rate is slowed in cells from male animals [28,78,79].

The Ca^{2+} chelator, EGTA, has been shown to reduce the rate of $I_{Ca\text{-}L}$ inactivation and normalize $I_{Ca\text{-}L}$ inactivation between old and young rats [79]. These authors suggest that EGTA should reduce Ca^{2+}-dependent inactivation and thus one possibility is that the age-associated slowing of $I_{Ca\text{-}L}$ inactivation is due to a decrease in Ca^{2+}-dependent inactivation [79]. This hypothesis is consistent with the general reduction in Ca^{2+} transient amplitude seen in the aged male heart, as discussed above. The lower peak $I_{Ca\text{-}L}$ would result in a smaller trigger for Ca^{2+}-induced Ca^{2+} release and may help explain the smaller Ca^{2+} transients seen in cells from older males. Then again, the slower inactivation of $I_{Ca\text{-}L}$ could lead to prolonged Ca^{2+} influx and increase the time course of the Ca^{2+} transient. This also would lengthen depolarization and could help explain the longer APD characteristic of the aging male heart. Prolonged Ca^{2+} influx may also act to load the aged SR with Ca^{2+} [92,93] and this effect is discussed in Section 5.1.

In contrast to males, little is known about the expression of L-type Ca^{2+} channels in aged female hearts. Only one study has explored this question and they found that L-channel protein expression was not affected by age in hearts from female rabbits [70]. Several studies have compared the amplitudes and characteristics of $I_{Ca\text{-}L}$ in myocytes from young adult and aged females (Table 4). Although one study found a decrease in peak $I_{Ca\text{-}L}$ with age [36] and one showed an increase [71], most investigations report that peak $I_{Ca\text{-}L}$ is not affected by age in cells from female animals [28,70,94]. Furthermore, there is no evidence that the inactivation rate of $I_{Ca\text{-}L}$ is slowed by age in female cells [28]. This result is consistent with the lack of change in Ca^{2+} transient amplitude in aged females and thus presumably unaltered Ca^{2+}-dependent inactivation. Together, these findings suggest that age has a marked effect on $I_{Ca\text{-}L}$ in cells from males, but little impact on this current in females.

4.3. Repolarizing currents in myocytes from aged animals

Whether an age-related decrease in repolarizing K^+ currents contributes to the longer APs seen in the aging male heart is controversial. Some studies report that peak transient outward current (I_{TO}) declines with age [79,95], while others report no change or even an increase in rat ventricular myocytes [75,78]. As I_{TO} plays a major role in repolarization in the rat ventricle [83], a decrease in the magnitude of this current would be expected to cause a marked prolongation in APD. Why this is not seen in all studies is unclear. There is evidence that the inward rectifier K^+ current (I_{K1}) increases with age [79], although this would be expected to cause faster repolarization [96]. Interestingly, a recent study demonstrated that the ATP-sensitive K^+ current (I_{KATP}) declines with age [81]. I_{KATP} is activated by falling ATP levels during metabolic stress such as ischemia and this leads to profound shortening of the cardiac AP [83], an effect thought to minimize Ca^{2+} overload in ischemia [97]. A reduction in I_{KATP} in the aging heart suggests that the ability to limit Ca^{2+} overload in ischemia may be compromised, though this would not explain prolongation of the APD in the absence of ischemia. The only study of K^+ currents in aging females used rabbits, where the slow delayed rectifier K^+ current (I_{Ks}) is a major repolarizing influence [83]. Results showed that age had no effect on I_{Ks}, I_{K1} or I_{TO} [70], which is consistent with reports that APD is not affected by age in female rabbits [70].

4.4. Impact of age on NCX

The electrogenic NCX primarily operates to remove one Ca^{2+} from the cell in exchange for three Na^+, which generates an inward current that helps maintain the plateau of the cardiac AP [98]. Whether NCX is modified by age has been investigated with both molecular and functional approaches (Table 4). While most laboratories report no age-dependent change in mRNA levels, protein expression or activity of the NCX in the male heart [12,31,32,44,80,82,90,99], others report a reduction [17,43,45,100–102]. Only one study has investigated NCX protein expression in the female heart and found no age-dependent change [70], so additional work in this area could be important. Although there is no evidence that intracellular Na^+ levels vary with age in males [80], functional studies have found that forward-mode NCX currents are enhanced in cells from aged male rats [82]. This depolarizing NCX current could contribute to the prolongation of the APD seen in myocytes from aged male rats. By contrast, there is no evidence that NCX currents are affected by age in female sheep, so enhanced inward NCX current is unlikely to contribute to prolongation of APD in this model [71].

5. Ca^{2+} sequestration and removal mechanisms in the aging heart

Given the critical role of the SR in intracellular Ca^{2+} release and reuptake, the influence of age on SR Ca^{2+} content and SR Ca^{2+} handling proteins has been the subject of extensive investigation. As with most studies of aging, the focus has been on hearts and myocytes from male animals.

5.1. SR Ca^{2+} uptake and SR Ca^{2+} content in myocytes from aged males

Table 5 summarizes the results of studies that have investigated the impact of age on processes involved in SR Ca^{2+} sequestration. There is virtually unanimous agreement that SR Ca^{2+} content is unaffected by age in males ([27,28,36,65,103] but *c.f.* [39]). Furthermore, mRNA and protein levels of the major SR Ca^{2+} binding protein, calsequestrin, are not influenced by age [32,39,55,65,82,104]. By contrast, there is emerging consensus that SERCA2a mRNA, protein and activity levels decline markedly with age in males [12,15,31,39,43–45,55,99,100,105,106], with a few studies reporting no change [17,65,68,90,104]. A decrease

Table 5
Age-dependent modifications in Ca^{2+} sequestration.

Sex	Component	Functional change[a]	Species	Reference[b]
Male	SR Ca^{2+} stores	↔ SR Ca^{2+} content	Rat	[36,65]
			Mouse	[27,28,103]
		↓ SR Ca^{2+} content	Rat	[39]
		↔ calsequestrin mRNA	Rat	[55]
		↔ calsequestrin protein	Rat	[39,65,82]
			Mouse	[32,104]
	SERCA2a	↓ SERCA2a mRNA	Rat	[55]
		↓ SERCA2a protein	Rat	[39,43,44,99,100]
			Mouse	[12,31]
		↓ SERCA activity	Rat	[45,105,106]
			Mouse	[15]
		↔ SERCA2a protein	Rat	[65]
			Mouse	[17,68,104]
			Rabbit	[90]
	PLB	↔ PLB protein	Rat	[39,44,45,65,99]
			Mouse	[31,32,104]
		↑ PLB protein	Rat	[43]
			Mouse	[17]
		↓ PLB protein	Mouse	[12]
	SERCA2a:PLB	↓ ratio	Mouse	[12,32]
Female	SR Ca^{2+} stores	↔ SR Ca^{2+} content	Rabbit	[70]
			Sheep	[71]
			Mouse	[28]
		↑ SR Ca^{2+} content	Rat	[36]
		↔ calsequestrin protein	Rabbit	[70]
	SERCA2a	↔ SERCA2a protein	Rat	[49]
			Rabbit	[70]
	PLB	↔ PLB protein	Rabbit	[70]

[a] Values are expressed relative to young adults (1–12 months of age for rats and mice; 5–9 months for rabbits; 18 months for sheep); aged rats and mice were between 20–31 months of age, older aged rabbits were 48–72 months and older sheep were >96 months.
[b] In some studies [15,17,39,45,55,68], the sex of the animals was not specified and is assumed to be male; in Howlett et al. [103] and Slack et al. [104] both males and females were used and results were pooled.

in SERCA activity and reduced SERCA2a protein expression would be expected to reduce the rate of Ca^{2+} uptake by the SR. This could account for the slowing of Ca^{2+} transient decay and prolonged relaxation rates characteristic of cardiomyocytes from older males (Tables 1 & 2). Not only do SERCA2a levels decline with age, but levels of its endogenous inhibitor, PLB, are either unchanged or actually rise ([17,31,32,39,43–45,65,99,104] but *c.f.* [12]). This would be expected to cause a decrease in the SERCA2a:PLB ratio with age, as recently demonstrated experimentally [12,32]. Reduced SERCA2a protein expression and lower SERCA2a:PLB ratio levels would slow SR Ca^{2+} uptake, which could explain the prolonged Ca^{2+} transient decay and slow relaxation characteristic of the aging male heart.

5.2. SR Ca^{2+} stores in cells from aged female animals

Comparatively, few studies have explored the influence of age on SR Ca^{2+} stores or SR Ca^{2+} handling proteins in the female heart (Table 5). Results of these investigations have shown that SR Ca^{2+} content is unaffected by age in rabbit, sheep and mouse models [28,70,71] but increases with age in the rat [36]. Furthermore, there is no age-dependent change in the expression of the major SR Ca^{2+} binding protein, calsequestrin, in the aged female heart [70]. Two studies have compared SERCA2a protein levels in young adult and aged females. They found no effect of age on SERCA2a expression levels in hearts from female rats and rabbits [49,70]. Furthermore, age has no effect on PLB expression levels in the female heart [70]. Together, these findings are consistent with previous reports that age has no impact on Ca^{2+} transient decay rates in female cardiomyocytes, although more studies of SR function and regulation in aged females are warranted.

5.3. Functional consequences of age-related changes in the SR

Along with SERCA, NCX plays a key role in decay of the Ca^{2+} transient because it removes Ca^{2+} from the cell on a beat-to-beat basis. As described earlier (Table 5), there is little agreement on whether NCX expression or activity is modified by age in the male heart and few studies have addressed this question in females. Functional studies have shown that Ca^{2+} removal by NCX is increased by age in myocytes from males [82]. This would be expected to speed decay of the Ca^{2+} transient rather than slow it, although increased removal by NCX could be countered by the age-dependent decrease in SR Ca^{2+} uptake by SERCA. By contrast, Ca^{2+} removal by NCX is not affected by age in females [71], which is consistent with reports that Ca^{2+} transient decay is unchanged. Whether age-dependent alterations in NCX expression and/or activity influence Ca^{2+} influx via reverse-mode NCX in aging has not yet been investigated. The direction of NCX depends upon the membrane potential and the concentration gradients for Na^{+} and Ca^{2+}, which are influenced by factors such as stimulation rate, external Ca^{2+} concentrations and species [48,107]. Thus, it may be difficult to compare results of functional studies of NCX conducted in different species under diverse experimental conditions.

Taken together, these data support the view that SERCA2a activity is reduced in hearts from aging male animals (Table 5). One might expect this to reduce SR Ca^{2+} content, but there is virtually no evidence that SR Ca^{2+} content changes with age in males. It is possible that SERCA activity is only impaired in aged cells at baseline and increasing Ca^{2+} by more rapid pacing may activate SERCA to normal levels via CAMKII (*e.g.* [60]). However, as discussed above, CAMKII (δ-isoform) levels and phosphorylation of PLB is decreased in the aged male heart which may affect responsiveness to increased rate. Alternatively, SR Ca^{2+} stores in males may be maintained by: i) reduced peak $I_{Ca\text{-}L}$, whereby a smaller trigger results in reduced Ca^{2+} release from the SR and less Ca^{2+} being lost from the cell [93] and ii) slower inactivation of $I_{Ca\text{-}L}$, if this results in increased Ca^{2+} loading via $I_{Ca\text{-}L}$ (and this remains to be tested). As such, applying a short AP to old rat cells augments peak $I_{Ca\text{-}L}$, reduces $I_{Ca\text{-}L}$ integral and decreases SR Ca^{2+} content [86], consistent with a smaller peak and larger integral of $I_{Ca\text{-}L}$ in the aged heart having a positive effect on SR Ca^{2+} load. Few studies have examined SERCA2a expression in older females, but those that have found no age-dependent decline. This is compatible with reports that SR Ca^{2+} content does not change (Table 5), although why SR Ca^{2+} content increases with age in female rats is not yet clear.

6. SR Ca^{2+} release mechanisms in the aging heart

As SERCA-mediated Ca^{2+} uptake declines with age while SR Ca^{2+} content is unaffected, some laboratories have investigated whether age affects Ca^{2+} sparks that act to regulate SR Ca^{2+} content. Still, only a few studies have examined mechanisms involved in SR Ca^{2+} release in hearts and myocytes from young adult and aged animals.

6.1. RyRs and Ca^{2+} sparks in the aging heart

One approach to explore the influence of age on SR Ca^{2+} release mechanisms has been to compare the density of SR Ca^{2+} release channels (RyR2) (Table 6). There is virtually unanimous agreement that age has no effect on expression of RyR2 protein in hearts from males and females ([31,32,39,65,70,99,105] but *c.f.* [100]). These data strongly suggest that the expression of SR Ca^{2+} release channels is not modified by age.

Ca^{2+} is released from the SR in the form of Ca^{2+} sparks that fuse to create the Ca^{2+} transient [25]. Therefore, some investigators have characterized spontaneous Ca^{2+} sparks to probe Ca^{2+} release mechanisms in aging heart (Table 6). Most studies have shown that Ca^{2+} spark duration, amplitude and width decline with age in both sexes [39,70,94], although one study found that only spark duration decreases with age [103]. There also is growing evidence that spontaneous spark frequency increases with age regardless of the sex of the animal ([39,94,103] but *c.f.* [70]). As elevated SR Ca^{2+} content increases the frequency of spontaneous Ca^{2+} sparks [108], the higher spark frequency in older females could be due to increased SR Ca^{2+} [36]. On the other hand, most studies in males and females have found that SR content is unaffected by age [27,28,36,65,70,71,103]. At present the reasons for the age-dependent decrease in the average size of Ca^{2+} sparks and increase in spark frequency are not clear but could involve post-translational modifications of RyRs as discussed in Section 6.2 below.

Table 6
Sr Ca^{2+} release mechanisms in the aging heart.

Sex	Component	Functional change[a]	Species	Reference[b]
Male	RyR2	↔ RyR2 protein	Rat	[39,65,99,105]
			Mouse	[31,32]
		↓ RyR2 protein	Rat	[100]
	Ca^{2+} sparks	↑ frequency	Rat	[39]
			Mouse	[103]
		↓ duration	Rat	[39]
			Mouse	[103]
		↓ amplitude	Rat	[39]
		↔ amplitude	Mouse	[103]
		↓ width	Rat	[39]
		↔ width	Mouse	[103]
Female	RyR2	↔ RyR2 protein	Rabbit	[70]
	Ca^{2+} sparks	↑ frequency	Rat	[94]
		↔ frequency	Rabbit	[70]
		↓ duration	Rat	[94]
		↓ amplitude	Rabbit	[70]
			Rat	[94]
		↓ width	Rabbit	[70]
			Rat	[94]

[a] Values are expressed relative to young adults (3–9 months of age for rats and mice; 5–9 months for rabbits; 18 months for sheep); aged rats and mice were between 24–28 months of age, older aged rabbits were 48–72 months and older sheep were >96 months.
[b] In studies by Zhu et al. [39] the sex of the animals was not specified and is assumed to be male; Howlett et al. [103] pooled cells from males and females.

6.2. Functional consequences of age-dependent changes in Ca^{2+} release mechanisms

As spark properties are modified by phosphorylation via the cAMP/PKA and CaMKII pathways [109–111], it is possible that age-dependent modifications in Ca^{2+} sparks are mediated by these routes. Indeed, cAMP levels are lower in ventricular myocytes from aged male rats compared to young adult controls [41]. While this could account for smaller Ca^{2+} sparks in the aging heart, it would not explain the increase in spark frequency with age ([39,103] but *c.f.* [70]). Age-associated changes in the CaMKII pathway also may be implicated, as CaMKII is activated by intracellular Ca^{2+}, which is modified by age in older males (Table 2). Furthermore, CaMKII δ protein expression declines in hearts from aged males and phosphorylation of RyR by CaMKII is reduced [65], which is compatible with smaller Ca^{2+} sparks in the aging heart [111]. Additional studies that explore these and other pathways involved in post-translational modifications of Ca^{2+} release mechanisms in the aging heart could be informative.

Several conclusions can be drawn from these studies of SR Ca^{2+} release mechanisms. The data presented above suggest that a decrease in the size of individual Ca^{2+} sparks is characteristic of the aging heart, regardless of the sex of the animal. On the other hand, spark frequency is increased with age. It is possible that the age-related decrease in spark size may offset the higher spark frequency to maintain SR Ca^{2+} load in the aging heart. Still, these smaller Ca^{2+} release units in conjunction with reduced peak $I_{Ca\text{-}L}$ may combine to produce smaller Ca^{2+} transients in the aging male heart. By contrast, there is no change in peak $I_{Ca\text{-}L}$ in aging female hearts, which may partially compensate for smaller Ca^{2+} release units and result in little or no attenuation of peak SR Ca^{2+} release.

7. Conclusions

Based on the evidence reviewed here, several conclusions can be made about the influence of age on cardiac EC-coupling mechanisms, as illustrated in Fig. 1. Contractions and Ca^{2+} transients are smaller and slower in ventricular myocytes from aged males compared to younger animals. The decrease in peak contractions and Ca^{2+} transients arises as a consequence of smaller peak $I_{Ca\text{-}L}$ and a reduction in the size of Ca^{2+} sparks in aging cardiomyocytes. Prolongation in the time-to-peak contraction likely reflects, at least in part, a decrease in myofilament Ca^{2+} ATPase activity in the aging heart. Relaxation is slowed due to an age-related shift to the slower β-MHC isoform, reduced phosphorylation of troponin I and slower Ca^{2+} transient decay. The slower rate of decay of the Ca^{2+} transient in aged cardiomyocytes is due to prolongation of the APD as well as a reduction in the SERCA2a:PLB ratio. In contrast to findings in males, there is little evidence that EC-coupling mechanisms are affected by age in cardiomyocytes from females. Peak contractions and Ca^{2+} transients are similar and there is little evidence for a reduction in peak $I_{Ca\text{-}L}$. Some studies suggest that APD and Ca^{2+} transient decay are prolonged in females, and the frequency of Ca^{2+} sparks increases with age, but spark size declines. These findings demonstrate that the aging process influences critical mechanisms involved in cardiac EC-coupling, although age-dependent remodeling differs between the sexes.

Reasons for male–female differences in cardiac aging are not yet known, but several factors may contribute. It is possible that age-dependent changes in sex steroid hormone levels contribute to the effects of age on cardiac EC-coupling mechanisms. It is well known that cardiomyocytes contain receptors for estrogen, progesterone and

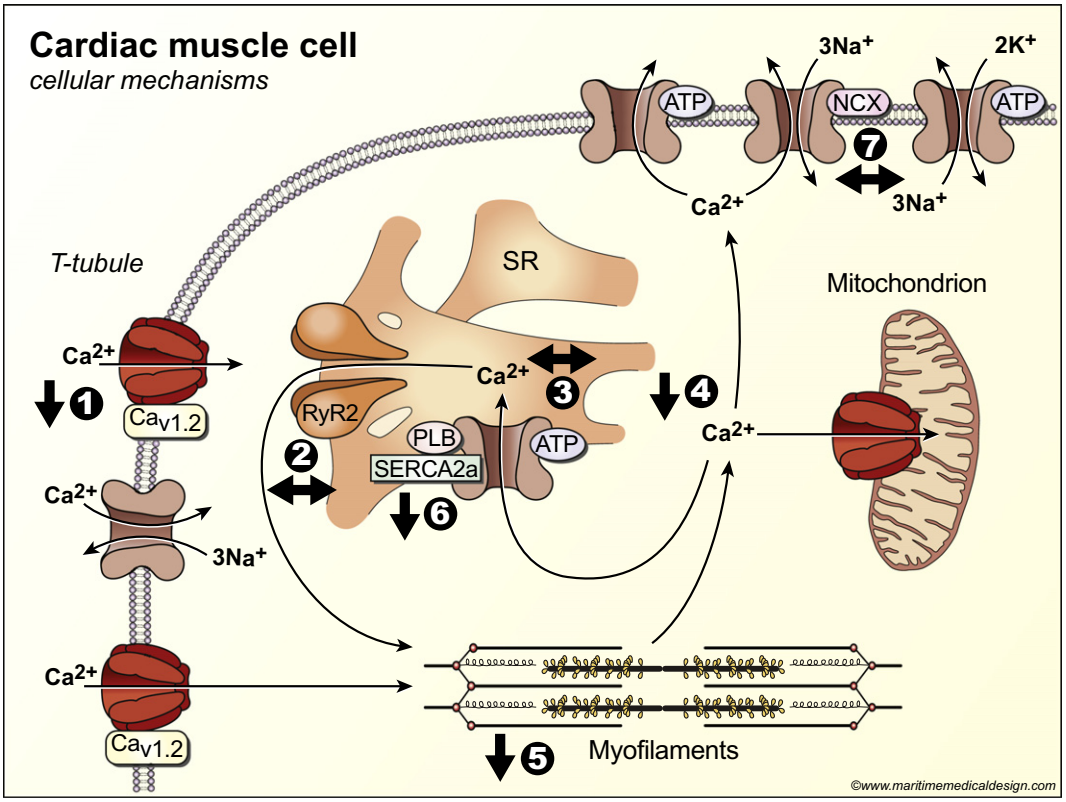

Fig. 1. Age-related changes in cardiac EC-coupling in isolated ventricular myocytes. A schematic diagram that illustrates the major sites of age-dependent changes in cardiac EC-coupling mechanisms in cardiomyocytes from male animals. 1. There is a decrease in peak $I_{Ca\text{-}L}$ and a slowing of inactivation of this current with age. 2. There is no change in RyR2 density, but Ca^{2+} spark frequency increases with age while the size of individual Ca^{2+} sparks declines. 3. SR Ca^{2+} content is not affected by age. 4. Ca^{2+} transients and contractions are smaller and slower in cardiomyocytes from aged males. 5. Age-related changes in myofilament proteins include a shift to the slower β-MHC isoform, reduced troponin I phosphorylation and a reduction in myofilament Ca^{2+} ATPase activity. 6. Ca^{2+} uptake by SERCA2a is slower in myocytes from aged animals when compared to younger adults, due to reduced expression of SERCA2a and a reduction in the SERCA2a:PLB ratio. 7. There is no clear pattern of change in NCX expression in the aging male heart, although Ca^{2+} extrusion by NCX may be enhanced. In contrast to these marked age-dependent changes in EC-coupling in the male heart, there is little evidence that age affects EC-coupling mechanisms in the female heart.

testosterone [73]. Experimental studies in young adult animals have shown that removal of the ovaries increases cellular Ca^{2+} transients and contractions [73]. Although less information is available, removal of the testes in young adult males prolongs contraction time in isolated myocytes [73]. These data suggest that sex steroid hormones can influence cardiomyocyte function. Interestingly, there is evidence that sex hormone levels decline with age in rodents as in humans. Female rats and mice undergo reproductive senescence and become anestrous (loss of the estrous cycle) between the ages of 12 to 18 months, depending upon the specific animal strain [112]. This is accompanied by a decline in circulating levels of estrogen and progesterone [113,114]. Similarly, testosterone levels decrease with age (>20 months) in male rodents in conjunction with a decline in fertility, while estrogen levels rise [115,116]. Thus, the effect of sex steroid hormones on cardiomyocytes may contribute to the age-related changes outlined in this review. It is also important to emphasize that, compared to males, relatively few studies have actually investigated the influence of age on cardiac EC-coupling mechanisms in female animals and many that have examined females have not evaluated age-matched males. More studies that investigate aging in both male and female models at the cellular, organ and intact animal levels could be illuminating.

8. Implications

As our population ages, the incidence of cardiovascular disease rises dramatically in both sexes, though there are important male–female differences in incidence, prevalence, presentation and outcomes associated with cardiovascular diseases [117,118]. For example, the incidence and prevalence of ischemic heart disease, the most common form of CVD, is higher in men than in women [118,119], although it rises markedly in women after menopause [120]. Paradoxically, while women with ischemic heart disease have less obstructive coronary artery disease than do men, they have more ischemia and higher mortality [121–123]. Although heart failure also occurs less often in women, their overall mortality rate is higher [117,124]. Men tend to develop heart failure with reduced ejection fraction, characterized by left ventricular dilatation and reduced wall thickness [125,126]. By contrast, women develop heart failure with preserved ejection fraction (HFpEF), characterized by normal left ventricular cavity size, increased wall thickness and diastolic dysfunction [125–127].

The observation that there are male–female differences in the way the heart ages at the cellular level has important clinical implications, since modifications in myocardial Ca^{2+} homeostasis and cardiac contraction are certain to interact with disease in the aging heart. For example, the observation that contractions and Ca^{2+} transients decline with age in males but not females may help explain why heart failure with reduced ejection fraction tends to occur in older men, while HFpEF is common in older women [126]. Furthermore, intracellular Ca^{2+} dysregulation is implicated in the pathogenesis of diseases such as myocardial ischemia and arrhythmias [128], where male–female differences are well known [118]. An increase in our understanding of the cellular mechanisms involved in the effect of age on both male and female hearts may help us understand why men and women are susceptible to different cardiovascular diseases as they age and may ultimately help identify new targets for intervention in the treatment of these diseases in both men and women.

Disclosures

None.

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Appendix A. Supplementary data

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