The impact of age on cardiac excitation-contraction coupling

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Summary

1. Cardiovascular diseases most commonly occur in the elderly and are a frequent cause of disability or death. However, the effect of age itself on cardiac function is not well understood.

2. Studies in both human and animal hearts indicate that contractile function is unaffected by age while at rest. However, the ability to increase cardiac contractile force during strenuous activities such as exercise declines with age.

3. Similar findings have been observed in individual ventricular myocytes isolated from aged hearts. When myocytes are stimulated with β-adrenergic agonists or rapid pacing frequencies, aged cells show a much smaller increase in peak contractions and Ca^{2+} transients than young adult cells. In addition, contractions and Ca^{2+} transients are prolonged in aged cells compared to younger cells under these conditions.

4. These observations suggest that the age-related decline in cardiac contractile function originates at the cellular level and may reflect modifications in processes involved in excitation-contraction (EC) coupling.

5. Biochemical studies have shown that there are age-related modifications in the expression, regulation and function of a number of proteins essential to EC-coupling in the heart.

6. Functional studies indicate that these changes in EC-coupling proteins disrupt Ca^{2+} homeostasis and contribute to decrease in peak contraction and prolongation of contraction duration observed in myocytes from aged hearts.

7. This review describes modifications in cardiac contractile function that occur in the ageing heart and evaluates underlying alterations in the EC-coupling pathway that may be responsible for this decline in contractile function in ageing.

Introduction

Most experimental studies of cardiovascular disease use young adult or even juvenile animals, which are very far removed from the human ages where cardiac pathophysiology becomes clinically important. However, the ageing process affects both the structure and function of the heart. This leads to an age-associated decline in cardiac function, which may predispose older adults towards the development of various cardiovascular diseases. To understand the impact of age on cardiac contractile function, effects of age on mechanisms involved in cardiac excitation-contraction (EC) coupling have been investigated at the level of the individual ventricular myocyte. This brief review describes our current understanding of the impact of age on cardiac contraction and evaluates underlying alterations to the EC coupling pathway that may provoke contractile decline in the ageing heart.

Contractile function in the ageing heart

In humans, ageing causes significant changes in the heart, even in the absence of overt cardiovascular disease.[1] Left ventricular wall thickness increases with age in the human heart.[1] This occurs even though the total number of viable ventricular myocytes actually declines with age because the remaining cells hypertrophy.[1,2] Increased accumulation of collagen and fibrous tissue also contributes to the thickening of the ventricle.[1] These structural changes are thought to contribute to the reduction in cardiac output and decrease in fractional shortening with age.[1,3] Although contractility at rest does not appear to be affected by age,[4-6] the ability to increase ejection fraction in response to activities such as exercise declines in older adults.[1] Myocardial contraction is also prolonged and relaxation is incomplete in aged individuals compared to younger adults.[1,7]

The impact of age on cardiac contractile function also has been investigated in various animal models of ageing. Most studies have used mice and rats that are approximately 24 months of age to model aged humans, and compared responses to data obtained in younger adult animals, typically aged 3 to 8 months. Based on survival data, the 50% mortality rate for humans occurs near the age of 85 years,[8] while the 50% mortality rate in mice and rats occurs at approximately 24 months of age.[9] Therefore, 24-month old rodents have been used as models of 85-year old humans.

Studies in aged rodent models have shown that left ventricular mass increases[10] and individual ventricular myocytes are hypertrophied across various species.[11-16] Also, the total number of ventricular myocytes decreases with age in the rat heart, likely as a result of an increase in necrotic and apoptotic cell death.[17] Contractile function also appears to change with age in animal models. In intact hearts and isolated cardiac tissues, peak contractions are unaffected by age at low stimulation rates, but fractional shortening declines with age and the rates of shortening and re-lengthening are prolonged at more rapid pacing rates.[18-27] A similar pattern is seen in *in vivo* studies when β-adrenergic receptors are stimulated to mimic the effects of exercise.[10,28] Aged hearts show a much smaller increase

in contractile force in response to β-adrenergic receptor stimulation than their younger counterparts. Since contractions are initiated by an increase in intracellular free Ca^{2+} at the level of the individual myocyte,[29] these observations suggest that contractile decline may result from impaired Ca^{2+} handling due to age-related modifications in components of EC-coupling.

Cardiac EC-coupling

Cardiac contraction is activated by a transient rise in intracellular free Ca^{2+}. The Ca^{2+} transient arises when Ca^{2+} influx, primarily as L-type Ca^{2+} current (I_{CaL}), triggers Ca^{2+} release from the sarcoplasmic reticulum (SR)[30] through Ca^{2+} release channels, known as cardiac ryanodine receptors (RyR).[31] This process is called Ca^{2+}-induced Ca^{2+} release (CICR).[32-34] Ca^{2+} release from the SR is proportional to the magnitude of I_{CaL}, and the degree to which this signal is amplified is known as the "gain" of CICR.[29] Experimentally, gain is defined as the amount of SR Ca^{2+} release divided by the amount of trigger Ca^{2+} influx (total Ca^{2+} release/I_{CaL}).[29] Gain can be modulated by temperature and by SR Ca^{2+} load[35,36] and is thought to play a role in the regulation of cardiac contraction.[37,38] During relaxation, most of the released Ca^{2+} is transported back into the SR by the SR Ca^{2+} ATPase (SERCA),[30] although some Ca^{2+} is removed from the cell by the Na^{+}/Ca^{2+} exchanger (NCX) with a minor contribution from the sarcolemmal Ca^{2+} ATPase.[39-41]

SR Ca^{2+} is released in discrete Ca^{2+} release units called Ca^{2+} sparks.[42-44] These Ca^{2+} sparks originate near specialized junctions between the sarcolemma (t-tubule or surface membrane) and the SR.[45-47] At these junctions, L-type Ca^{2+} channels and RyRs are located in close proximity.[45-47] Ca^{2+} sparks are thought to represent coordinated Ca^{2+} release through a cluster of RyRs which become activated by one or more L-type Ca^{2+} channels.[29,45,48] Normally, spontaneous Ca^{2+} release from one release unit does not activate neighbouring release units, as released Ca^{2+} diffuses away from adjacent units.[29] However, upon depolarisation, many release units are simultaneously activated by I_{CaL} and individual Ca^{2+} sparks fuse to form the Ca^{2+} transient.[29,49] Spontaneous Ca^{2+} sparks also can occur in quiescent cells, even in the absence of L-channel openings.[42,44,50] Spark frequency increases as SR Ca^{2+} load increases, which suggests that spontaneous Ca^{2+} sparks represent a leak pathway for Ca^{2+} that limits SR Ca^{2+} content.[51] Thus, changes in these unitary Ca^{2+} release events can impact upon SR Ca^{2+} content and affect the magnitude of the Ca^{2+} transient.

Since the cardiac contraction largely reflects the magnitude and time course of the Ca^{2+} transient,[52,53] processes which affect the Ca^{2+} transient have clearly been of interest in studies of the impact of age on cardiac contractile function. Many studies have focussed on the effect of age on contractions and Ca^{2+} homeostasis at the level of the individual ventricular myocyte. As described in detail below, ageing results in significant biochemical and physiological changes in the EC-coupling pathway that are believed to be linked to the decline in contractile function in the ageing heart.

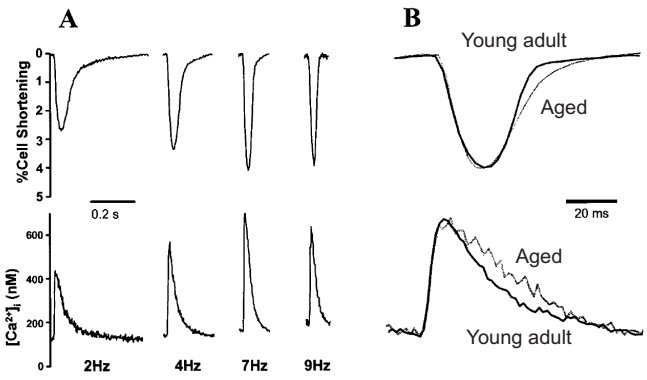

Figure 1. Contractions and Ca^{2+} transients are prolonged at rapid stimulation rates in ventricular myocytes from aged mice compared to cells from younger animals. A: *Contractions and Ca^{2+} transients were recorded from myocytes isolated from young adult (5 mo) and aged (34 mo) mice. Cells were loaded with fura-2 and field-stimulated at a range of different frequencies at 37°C. Representative recordings of cell shortening (top) and Ca^{2+} transients bottom) from a young adult myocyte paced at 2, 4, 7, and 9 Hz.* ***B:*** *Examples of contractions (top) and Ca^{2+} transients (bottom) recorded from young adult and aged myocytes paced at 9 Hz. Responses were normalized to the peak value in each case to show changes in time course. Each recording represents the average of ten original recordings. Reprinted from Lim* et al.[14] *with permission.*

EC-coupling in the ageing heart

Contractile function in ventricular myocytes from aged animals

A decrease in the ability of individual ventricular myocytes to contract is thought to contribute importantly to the age-associated decline in cardiac contractile function. When myocytes are paced at slow stimulation rates (<1 Hz), peak contractions appear similar in young adult and aged myocytes from mice and rats.[13,14,54,55] However at higher stimulation frequencies (> 2 Hz), the extent of cell shortening is lower in aged mouse ventricular myocytes than in young adult cells.[14] In addition, re-lengthening is prolonged in cells from aged animals.[14] The decline in cardiac contractile function also is reflected in Ca^{2+} transients recorded from aged rodent myocytes.[13,14,56] Figure 1 shows results from a study by Lim *et al.*[14] that compares contractions and Ca^{2+} transients recorded from ventricular myocytes isolated from young adult and aged mice. In young adult myocytes, peak contractions and Ca^{2+} transients increase and responses decay more rapidly at higher stimulation frequencies[14,56] (Figure 1A). However, aged myocytes produce much smaller increases in peak Ca^{2+} transients than younger cells when myocytes are paced at rapid rates.[14,56] In addition, rates of decay are prolonged

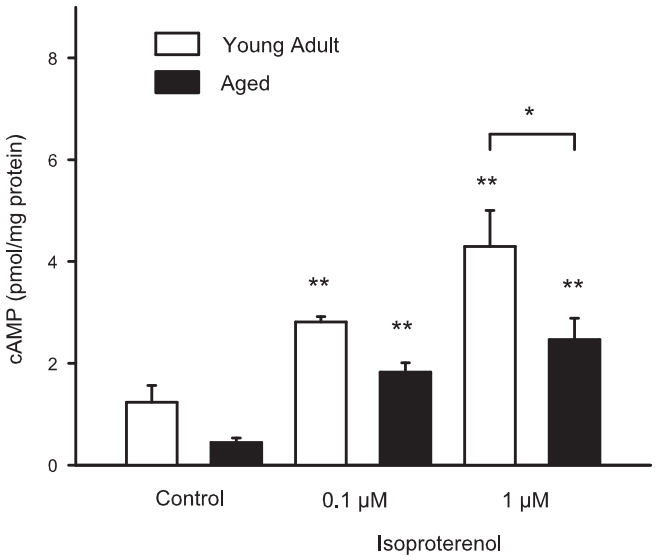

Figure 2. Intracellular cAMP formation in response to increasing concentrations of the non-selective β-adrenergic agonist isoproterenol was significantly greater in ventricular myocytes from young adult rats compared to myocytes from aged rats. *Intracellular cAMP formation was measured in isolated intact ventricular myocytes isolated from young adult (3 mo) and aged (24 mo) rats. Intracellular cAMP production in response to administration of isoproterenol was increased over control levels in both young adult and aged myocytes. However, this increase was significantly greater in young adult myocytes when compared to aged cells (** denotes significantly different from age-matched control group, $p < 0.05$; * denotes significantly different from young adult group, $p < 0.05$). Reprinted from Farrell & Howlett[57] with permission.*

in aged cells when compared to younger cells under these experimental conditions[14,56] (Figure 1B). These results suggest that the ability of individual ventricular myocytes to contract declines with age. This functional decline at the level of the myocyte would be expected to decrease the overall contractile performance of the ageing heart.

Ventricular myocytes from aged animals also show a decrease in their ability to augment contractions and Ca^{2+} transients when β-adrenergic receptors are stimulated by catecholamines.[13,55,57] In addition, the rates of decay of contractions and Ca^{2+} transients are prolonged in aged cells when compared to younger cells in the presence of β-adenergic receptor stimulation.[13] This may be due to a decrease in the density of β-adrenergic receptors with age,[58] though most studies have reported no effect of age on β-adrenergic receptor density.[59-61] Recently however, Farrell & Howlett[57] reported that a decrease in adenylate cyclase activity with age leads to less cAMP production in ventricular myocytes from aged rats.[57] Figure 2 shows that, when ventricular myocytes are stimulated with the non-selective β-agonist isoproterenol, aged cells produce significantly less cAMP than younger cells.[57] This decrease in β-adenergic receptor signalling may help explain the loss of sensitivity to catecholamines that occurs with age. These age-associated modifications in contractions, Ca^{2+} transients and β-adrenergic receptor signalling in various animal models of ageing are summarized in Table 1.

Molecular components of EC-coupling in the ageing heart

To understand mechanisms that suppress contractile function in the ageing heart, a number of studies have investigated the impact of age on proteins involved in EC-coupling. Contractions are slowed in the ageing heart, in part due to changes in myofilament proteins including a shift from α myosin heavy chain to β myosin heavy chain.[62] This results in a decrease in myosin ATPase activity in the ageing heart.[62] Changes in SERCA2a, the primary SERCA isoform expressed in the heart, also may affect relaxation in the ageing heart. An age-related decrease in the ability of SERCA2a to sequester Ca^{2+} in the SR may prolong the Ca^{2+} transient and slow contraction in the ageing heart.[20,22,63] Reduced expression of SERCA2a in aged myocytes may be responsible for the slowing of Ca^{2+} reuptake and prolongation of contraction,[63] although this is controversial.[62,64,65] Age-related modifications in the regulation of SERCA2a by the endogenous inhibitor phospholamban (PLB) also may affect contraction in the ageing heart. PLB is expressed at elevated levels in aged mice,[64] which would be expected to slow Ca^{2+} reuptake in the ageing heart. Furthermore, phosphorylation of PLB by protein kinase A (PKA) appears to decrease with age.[65] As phosphorylation of PLB by PKA normally increases the activity of SERCA2a and speeds relaxation,[66] a reduction in phosphorylation of PLB by PKA would slow contraction in the ageing heart. Further, the ability of Ca^{2+}/calmodulin dependent (CaM) kinase to increase SERCA2a activity through phosphorylation is reduced in the ageing heart.[65] Together, these findings indicate that SERCA2a activity may be decreased in the ageing heart due to a decline in pump density and an increase in inhibitory regulation. These changes would be expected to slow SR Ca^{2+} uptake, reduce SR Ca^{2+} content and prolong the Ca^{2+} transient, all of which would contribute to a decline in contractile function in the ageing heart.

Other studies have investigated NCX activity in the ageing heart. Results of studies with membrane vesicles or cardiac muscles have been inconsistent, with reports that NCX activity is either decreased[64,67] or unchanged[68] in the ageing heart. The reasons for these diverse results are unclear, but might be due to differences in membrane preparations or experimental models. However, a recent study of the function of NCX has shown that NCX activity actually increases with age in intact ventricular myocytes.[69] As NCX functions primarily to remove Ca^{2+} from the cell, an increase in NCX activity might help remove Ca^{2+} from the ageing cardiac myocyte during relaxation. This could serve to compensate, at least in part, for the age-related decline in SERCA2a activity. The increased expression of NCX also may enhance Ca^{2+} influx during the action potential, which may contribute to the prolonged

Table 1: Age-associated decline in contractile function and β-adrenergic receptor signalling in ventricular myocytes

Parameter	Functional Change	Model/References
Contraction	↓ cell shortening, relaxation slowed, w/ rapid stimulation	mice, 5 *vs* 24 & 34 mo;[14]
Contraction	↓ cell shortening, relaxation slowed w/ β-AR stimulation	rats, 1-4 *vs* 24 mo;[13] 3 mo *vs* 24 mo[55,57]
Ca^{2+} Transient	↓ peak amplitude, decay slowed, w/ rapid stimulation	mice, 5 *vs* 24 & 34 mo;[14] mice, 2 *vs* 20-26 mo[56]
Ca^{2+} Transient	↓ peak amplitude, decay slowed, w/ β-AR stimulation	mice, 5 *vs* 24 & 34 mo;[14] mice, 2 *vs* 20-26 mo[56]
β-AR signalling	↔ receptor density	rats, 3 *vs* 24 mo;[59] rats, 3 *vs* 24 mo;[60] rats, 3 *vs* 24 mo[61]
	↓ receptor density	rats, 2 *vs* 24 mo[58]
	↓ cAMP production	3 mo *vs* 24 mo[57]

Abbreviations: β-adrenergic receptor (β-AR)

Table 2: Molecular components of the EC-coupling pathway in the ageing heart

Component	Modification	Model/references
Myosin ATPase	↓ATPase activity	rats, 4 *vs* 24 mo[62]
	α to β myosin heavy chain	rats, 4 *vs* 24 mo[62]
SERCA2a	↓ sequestration of Ca^{2+}	rats, 6-8 *vs* 24-26 mo;[20] rats, 1-2 *vs* 24 mo;[63] rats, 6-8 *vs* 24-26 mo[22]
	↓ expression	rats, 1-2 *vs* 24 mo[63]
	↔ expression	rats, 6-8 *vs* 26-28 mo;[65] mice, 5 *vs* 24 & 34 mo;[64] rats, 4 *vs* 24 mo[62]
	↓ phosphorylation	rats, 6-8 *vs* 26-28 mo[65]
PLB	⇑ protein expression	mice, 5 *vs* 24 & 34 mo[64]
	↓ phosphorylation	rats, 6-8 *vs* 26-28 mo[65]
NCX	⇑ activity	14-15 *vs* 27-31 mo[69]
	↔ or ↓ activity	mice, 5 *vs* 24 & 34 mo;[64] rats, 6 *vs* 24 mo;[68] rats, 4-6 *vs* 24-27[67]
Calsequestrin	↔	rats, 1-2 *vs* 24 mo;[63] mice, 5 *vs* 24 & 34 mo[64]
RyR	↓ Receptor density	rats, 4 vs. 24 mo;[18] hamsters, 4 *vs* 10 mo[70]
	↔ density	rats, 6-8 *vs* 26-28 mo[65]
	↓ phosphorylation	rats, 6-8 *vs* 26-28 mo[65]

Abbreviations: Ryanodine receptor (RyR); cardiac SR Ca^{2+} ATPase (SERCA2a); phospholamban (PLB); Na^{+}/Ca^{2+}exchanger (NCX).

contraction observed in aged myocytes.[7] However, the relative contributions of NCX and SERCA2a to myocardial relaxation in the ageing heart remain uncertain.

Proteins involved in SR Ca^{2+} release have also been investigated in the ageing heart. Levels of calsequestrin, the major SR Ca^{2+} binding protein, are similar in young adult and aged hearts.[63,64] In contrast, proteins involved in SR Ca^{2+} release have been shown to change with age. Changes in RyR2, the major RyR expressed in heart, also may affect contractile function in the ageing heart. Some studies have observed an age-associated reduction in RyR2 levels in the ageing heart,[18,70] although this has not been reported in all models of ageing.[65] In addition, phosphorylation of RyR2 by CaM kinase is reduced in the ageing heart.[65] The physiological consequences of phosphorylation of RyR2 remain highly controversial,[71] but the decrease in phosphorylation of RyR2 with age may affect SR Ca^{2+} release in the ageing heart. The major age-associated modifications in components of cardiac EC coupling in different animal models of ageing are illustrated in Table 2.

Functional studies of components of EC coupling in aged ventricular myocytes

To determine whether age-related modifications in proteins affect cardiac function, physiological properties of ventricular myocytes have been compared in cells from young adult and aged animals. Some studies have explored the impact of age on spontaneous Ca^{2+} sparks to establish whether the decrease in RyR2 density and reduction in RyR2 phosphorylation might affect unitary Ca^{2+} release events. Studies have shown that the frequency of spontaneous Ca^{2+} sparks increases with age in mouse ventricular myocytes, although the duration of individual Ca^{2+} sparks declines.[72] An increase in spark frequency along with a reduction in Ca^{2+} spark duration also has been reported in aged rat myocytes, along with a decline in the width and amplitude of Ca^{2+} sparks.[73] These findings suggest that age-associated changes in RyR2 may affect

Table 3: Functional studies of EC coupling in aged ventricular myocytes

Parameter	Functional Change	Model/references
Ca^{2+} Sparks	⇑ spontaneous spark frequency	mice, 5 *vs* 24 mo;[72] rats, 6 *vs* 24 mo[73]
	↓ spark duration	mice, 5 *vs* 24 mo;[72] rats, 6 *vs* 24 mo[73]
	↓ spark width	rats, 6 *vs* 24 mo[73]
	↓ spark amplitude	rats, 6 *vs* 24 mo[73]
Action Potential	⇑ duration	rats, 6-8 *vs* 24-26 mo;[22] rats, 2-3 *vs* 24-25 mo;[12] rats, 6 *vs* 27+ mo[15]
RMP	↔ RMP	rats, 6-8 *vs* 24-26 mo;[22] rats, 2-3 *vs* 24-25 mo;[12] rats, 6 *vs* 27+ mo[15]
I_{TO}	↓ peak current density	rats, 2-3 *vs* 24-25 mo[12]
	↓ rate of inactivation	rats, 6 *vs* 27+ mo[15]
NCX	⇑ forward mode current	rats, 14-15 *vs* 27-31 mo[69]
I_{CaL}	↓ rate of inactivation	rats, 6 *vs* 27+ mo;[15] rats, 2-3 *vs* 24-25 mo;[12] mice, 7 *vs* 24 mo[75]
	↓ peak current density	rats, 6 *vs* 27+ mo;[15] mice, 7 *vs* 24 mo[75]
	↓ Ca^{2+} channel density	hamsters, 4 *vs* 20 mo[74]

Abbreviations: L-Type Ca^{2+} channel current (I_{CaL}); transient outward K^+ current (I_{TO}); Na^+/Ca^{2+}exchanger (NCX); resting membrane potential (RMP).

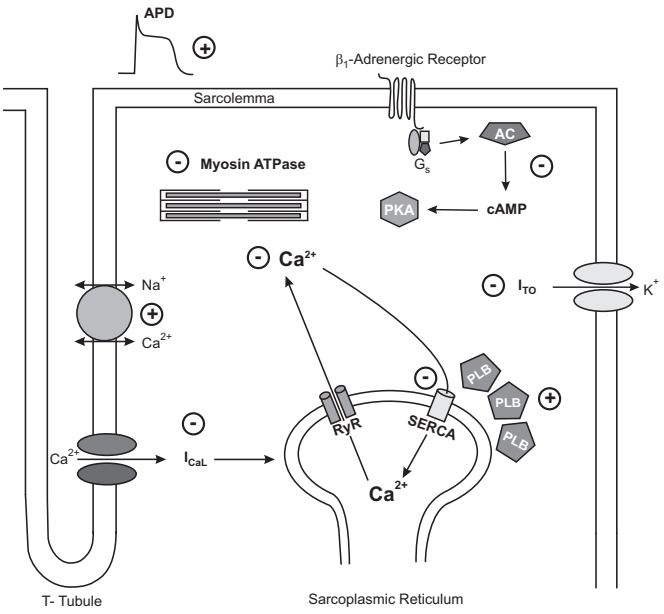

Figure 3. Changes in major components of cardiac excitation-contraction coupling in the ageing heart*. In the ageing heart, action potential duration, contraction duration, and Ca^{2+} decay rate are all prolonged. These changes occur as a result of reduced Ca^{2+} influx, reduced Ca^{2+} release, and depressed cardiac contractile efficiency, due to a decline in expression or activity, of proteins involved in cardiac EC coupling. An age-related decrease in the effect of β-adenergic stimulation, due to a reduction in cAMP production in the ageing heart also are seen. Alterations in these mechanisms are thought be responsible for the cardiac contractile decline observed in ageing heart.*

Ca^{2+} spark activity and Ca^{2+} spark properties in the ageing heart. A reduction in spark duration and/or spark widths and amplitudes might be expected to disrupt SR Ca^{2+} release in the ageing heart. In addition, increased Ca^{2+} spark activity in ageing cardiac myocytes may reduce SR Ca^{2+} content and disrupt Ca^{2+} transients in the ageing heart.

Other studies have investigated electrophysiological properties of intact ventricular myocytes isolated from young adult and aged animals. Studies have shown that the cardiac action potential, which initiates the Ca^{2+} transient, is prolonged in the ageing heart.[12,15,22] On the other hand, resting membrane potentials in ventricular myocytes and tissues are not affected by age.[12,15,22] Voltage clamp studies have shown that the increased action potential duration in the ageing heart results from age-dependent changes in transmembrane currents. Ageing is associated with a decrease in peak density of the repolarising transient outward K^+ current (I_{TO}) and a modest slowing of the rate of inactivation of I_{TO}.[12,15] Forward-mode NCX current also increases with age.[69] The inactivation of I_{CaL} also is slowed in aged rat ventricular myocytes compared to younger cells.[12,15] Collectively, the decrease in I_{TO}, increase in inward NCX current and slowed inactivation of I_{CaL} can account for the increase in action potential duration observed in aged ventricular myocytes.[22] This increase in action potential duration would be expected to prolong depolarisation and could slow Ca^{2+} release and contractions in aged cardiac myocytes. Interestingly, many previous studies that reported prolongation of Ca^{2+} transients and contractions in ageing myocytes were conducted in field-stimulated cells, where Ca^{2+} release and contractions were activated by action potentials.[13,14,55] Thus, it is possible that the age-related increase in action potential duration contributes to the slowed contractions and prolonged Ca^{2+} release reported in these studies.[13,14,55] Key findings of functional studies of cardiac EC coupling in rodent models of ageing are summarized in Table 3 and illustrated in Figure 3.

Studies have shown that peak density of I_{CaL} declines with age in rat ventricular myocytes, at least when experiments are conducted under physiological conditions.[15] Receptor binding studies also have shown that the density of dihydropyridine receptors (L-type Ca^{2+} channels) declines with age, although properties of these

channels are unchanged.[74] As I_{CaL} is the predominant trigger for CICR, the observed decrease in I_{CaL} may account for the reduction in SR Ca^{2+} release and decrease in the size of contractions reported previously in aged myocytes.[13,14,56] However, these previous studies of contractile function in ventricular myocytes did not measure I_{CaL} together with contractions and/or SR Ca^{2+} release. A recent study used voltage clamp techniques to directly investigate effects of age on contractions, Ca^{2+} transients and transmembrane currents.[75] With voltage clamp techniques, the duration and magnitude of depolarisation can be controlled and variations in action potential duration can be eliminated. Under these conditions, the amplitudes of contractions and Ca^{2+} transients are smaller in ventricular myocytes from aged mice (~24 mo) compared to responses in cells from young adult animals (5-6 mo).[75] However, this study also showed that the age-related decline in the size of contractions and Ca^{2+} transients occurred only in myocytes from male animals and not in cells from female animals.[75] These findings suggest that age-related changes in cardiac EC-coupling may be more prominent in myocytes from males than in cells from females. Consistent with this idea, another study in ventricular myocytes from female sheep reported no evidence of contractile decline with age.[16] However, most other studies of the impact of age on cardiac EC-coupling have used hearts and myocytes from male animals only or the sex of the animals has not been specified. As a result, most changes considered "typical" of the ageing process reflect observations in hearts and myocytes from male animals. This is an intriguing finding that suggests the impact of age on cardiac EC coupling is markedly affected by the sex of the animal. Further research considering sex as a variable may improve understanding of how the heart changes with age in men and women, and may help explain sex differences in the expression of various cardiovascular diseases.

Summary

Age-related modifications in cardiac structure and function contribute to the decline in cardiac contractile function associated with ageing. Although this is not evident at rest, stimuli that augment contractile function are less effective in aged hearts than in young adult hearts. At the cellular level, contractions are smaller and slower in aged myocytes than in younger cells when myocytes are exposed to rapid pacing rates or β-adrenergic agonists. Evidence suggests that this decline in contractile function originates from modifications in the expression, regulation, and function of proteins associated with myocardial Ca^{2+} handling. An age-related reduction in the density and activity of RyRs may contribute to this decline. A decrease in SERCA expression, activity and function as well as an increase in SERCA inhibition by PLB also could play a crucial role in slowing contraction. A decrease in I_{TO}, increase in inward NCX current and prolongation of the inactivation of I_{CaL} may increase action potential duration and slow contraction in aged ventricular myocytes. In addition, reduced L-type Ca^{2+} channel density and a decrease in peak I_{CaL} may suppress CICR, which would depress cardiac contraction. Further investigation of these age-related changes should help explain why cardiac contractile function declines with age. Studies in animals of both sexes may reveal important sex differences in the effects of age in the heart, which might help explain why men and women develop different heart diseases later in life.

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