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Reduced Cardiac Response to the Adrenergic System is a Key Limiting Factor for Physical Capacity in Old Age.

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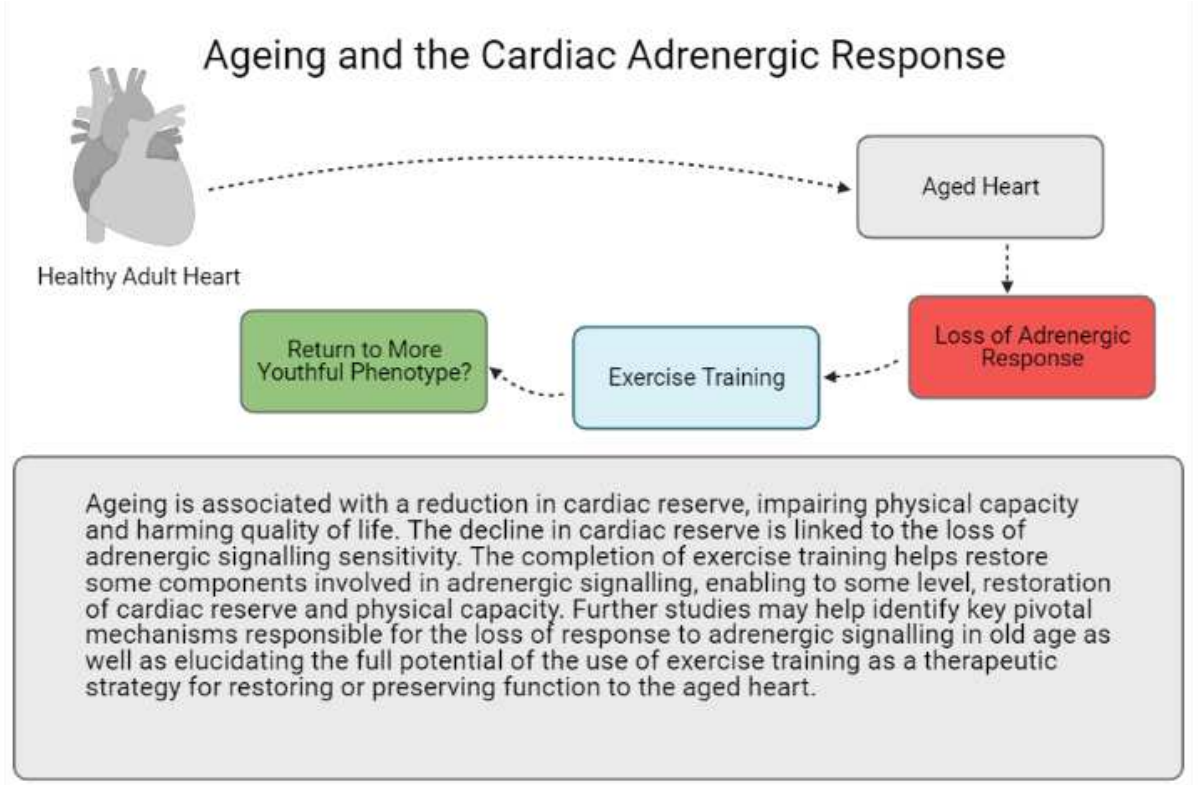
Abstract



Graphical abstract created using BioRender.

Ageing is associated with a progressive reduction in physical capacity reducing quality of life. One key physiological limitation of physical capacity that deteriorates in a progressive age-dependent manner, is cardiac reserve. Peak cardiac output falls progressively with advancing age such that in extreme old age there is limited ability to enhance cardiac output beyond basal function as is required to support the increased metabolic needs of physical activity. This loss of dynamic range in cardiac output associates with a progressive reduction in the heart's response to adrenergic stimulation. A combination of decreases in the expression and functioning of beta1 adrenergic receptors partially underly this change. Changes in end effector proteins also have a role to play in this decline. Alterations in the efficiency of excitation-contraction coupling contribute to the reduced chronotropic, inotropic and lusitropic responses of the aged heart. Moderate to vigorous endurance exercise training however has some potential to counter elements of these changes. Further studies are required to fully elucidate the key pivotal mechanisms involved in the age-related loss of response to adrenergic signalling to allow targeted therapeutic strategies to be developed with the aim of preserving physical capacity in advanced old age.

Keywords

Ageing, β_1 adrenergic receptors, Cardiac reserve, Cardiac output, Adrenergic desensitisation, Exercise.

Article Highlights

- Progressive reductions in exercise tolerance and cardiac reserve are associated with increasing age potentially producing a limit to functional lifespan.
- A reduction in response to adrenergic stimulation is a key mechanism underlying the age-related reduction in the dynamic range of cardiac output.
- Reductions in the dynamic range of the heart rate as well as contractile function are both key.
- Exercise training offers a potential means for preserving or restoring adrenergic responsiveness in old age.

Abbreviations

AC: Adenylyl cyclase

AP: Action potential

APD: Action potential duration

ATP: Adenosine tri-phosphate

β_1AR: Beta 1 adrenergic receptor

Ca^{2+}: Calcium

CaMKⅡ: Ca^{2+}/ calmodulin-dependent protein kinase

cAMP: Cyclic adenosine ‘3, ‘5 monophosphate

CICR: Calcium-induced calcium release

CO: Cardiac output

EDV: End-diastolic volume

GRK: G-protein receptor kinase

HCN: Hyperpolarisation-activated cyclic nucleotide-gated cation channels

HR: Heart rate

I_f: Funny current

Ik_s: Slowly activating delayed rectifier potassium channel

KATP: ATP-sensitive potassium channel

LTCC: L-type calcium channel

NCX: Sodium: calcium exchange channel

PDE: Phosphodiesterase

PKA: Protein kinase A

PLN: Phospholamban

ROS: Reactive oxygen species

RyR2: Ryanodine type 2 receptor

SAN: Sino-atrial node

SERCA2a: Sarco/endoplasmic reticulum Ca^{2+}-ATPase

SNS: Sympathetic nervous system

SR: Sarcoplasmic reticulum

SV: Stroke volume

Tn_i: Troponin i

1.0 Introduction

Cardiac reserve reflects the difference between basal cardiac output (CO) and maximal CO, and is a good indicator of cardiac health [5, 21-26]. In the last fifty years average life expectancy has increased significantly, however age-related reductions in cardiac function are ubiquitously observed with no evidence to suggest this age-related reduction is changing in terms of its rate of progressive onset [27, 28]. Formulae such as 220-age (in years) are commonly used to predict maximal attainable heart rate (HR) approximating the typical gradient of decline in the dynamic range available, but this fall in maximum attainable HR (Figure 1) is not the sole cause of the reduction in peak CO and dynamic range (~10-25%)[9, 29, 30]. Stroke volume (SV) also becomes impaired with advancing age (~10-20%) (Figure 3) [6, 29-31]. The logical inference of this progressive fall in peak CO is that by an age of approximately 125-135 years, there would be no scope for an individual to cope with any activity beyond basic metabolic support of the body at rest. Indeed this corresponds well with maximum currently recorded longevity (Jeanne Calment, aged 122 years at death) and the results of work suggesting a current limitation to ~125 years [32]. This deterioration then presents a limitation to human lifespan overall and certainly the functional ability to participate in sustained physical activity and activities of daily living at earlier ages (Figure 1).

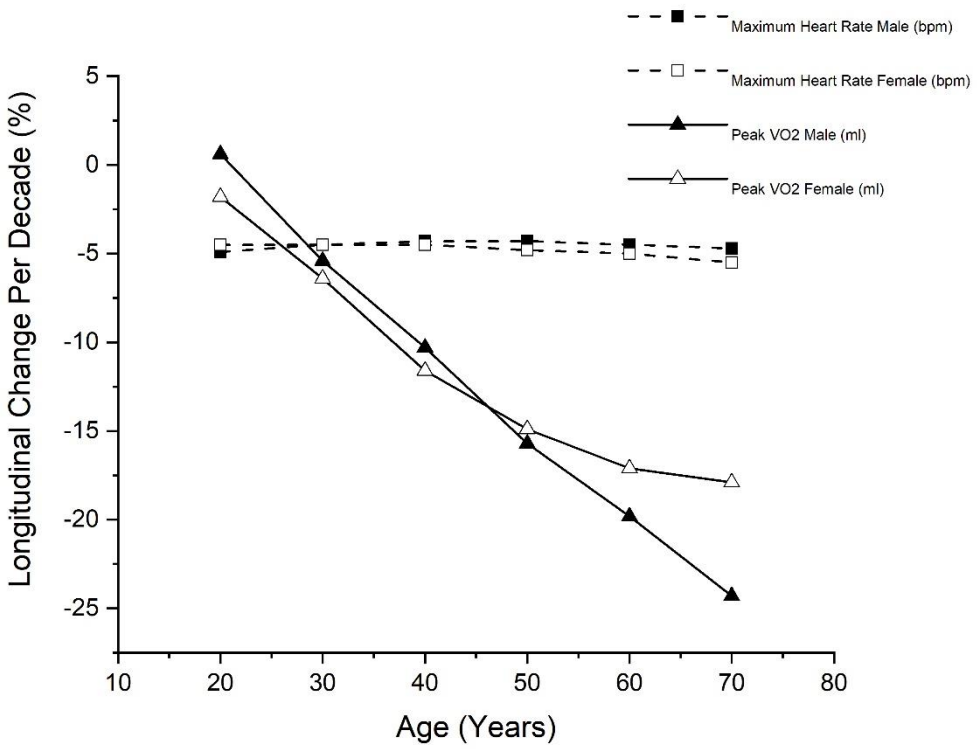


Figure 1. Percentage longitudinal decline in maximal HR and peak V_{O_2} in males and females per decade of life. Figure adapted from Fleg et al. (2005) utilising data from the "Baltimore Longitudinal Study of Aging" [8, 10-12].

Reduced ability to respond to and cope with physical activity is a considerable burden to the health of elderly populations [27, 33]. It was estimated 3.5 million older people in the UK in 2015 have difficulty or complete inability to perform at least 1 normal activity of daily living such as climbing stairs or getting dressed [34]. This figure is expected to grow exponentially in years to come, as a result of the disparity between lifespan and healthspan [34-36]. The effect of age on mobility and physical capacity is exemplified by reductions in walking speed (30%, 70-80y vs 20-30y) [37], 6-minute walk [36] and 2-minute step test performance (11%) as well as sit-to-stand repetitions during standardised testing (12% decrease) in old compared to younger adults [35, 36].

Whilst a cascade of components may contribute to the development of the aged heart phenotype (Summarised in Figure 2) [27, 38], the predominant focus of this review is the change in adrenergic response and associated cardiac reserve during ageing, thus some changes listed in Figure 2 are not discussed further. Although for further information please see references [1-8].

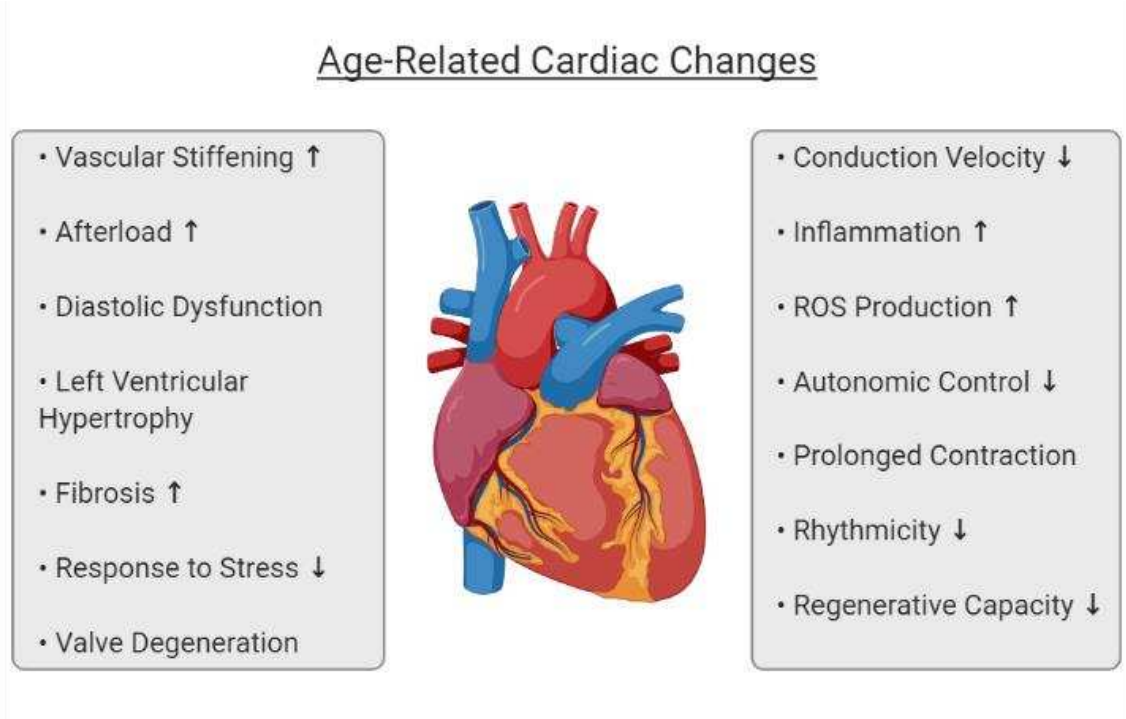


Figure 2. Cardiac changes commonly observed in aged hearts [1-9]. Figure generated using BioRender.

1.1 Determinants of Cardiac Output

Cardiac output, defined as the amount of blood pumped from the heart in one minute, is mediated by SV and HR [6, 39]. Decrements in CO and CO reserve observed in old age are heavily dependent on separate age-related changes in HR and SV (Figure 1, Figure, 2) [6].

1.1.1 Ventricular Inotropy and Cardiac Output Changes in Advanced Age

Age-related changes in ventricular inotropy compared to HR have been suggested to have a greater influence on exercise response in CO in old age even though the age-dependent change in HR is the parameter most people are familiar with [6, 40]. Reductions in SV were found in one study to account for 66% of the overall reduction in CO (~21-25%) observed in old age compared to adults during exercise (Figure 3) (~63 vs ~27y) [9]. Meanwhile, the HR reduction contributed to just 26-30% of the overall reduction in CO in aged hearts during exercise [9]. Age-related alterations in inotropic responses to exercise are complex and associate with reduced adrenergic responsiveness which explain reductions in peak CO [11, 27, 41, 42]. In old age, in contrast to young adults upon exercise, SV is understood to function predominantly in line with the “Frank-Starling mechanism” as opposed to sympathetic nervous

system (SNS) involvement [43]. Enhanced left ventricular end-diastolic volume size, caused by reduced early diastolic filling and increased atrial involvement and increased late filling, elevates the stretch-induced increase in contractile force helping maintain CO during exercise [43]. This can place greater strain on the aged heart, increasing the vulnerability of the entire system upon onset of conditions like atrial fibrillation. It also indicates the aged hearts reliance on greater chamber size to cope with changes in demand, which contradicts the efficiency of the use of cardiac reserve. Such changes in the provision of SV in old compared to young adults indicate a significant breakdown of normal adrenergic signalling.

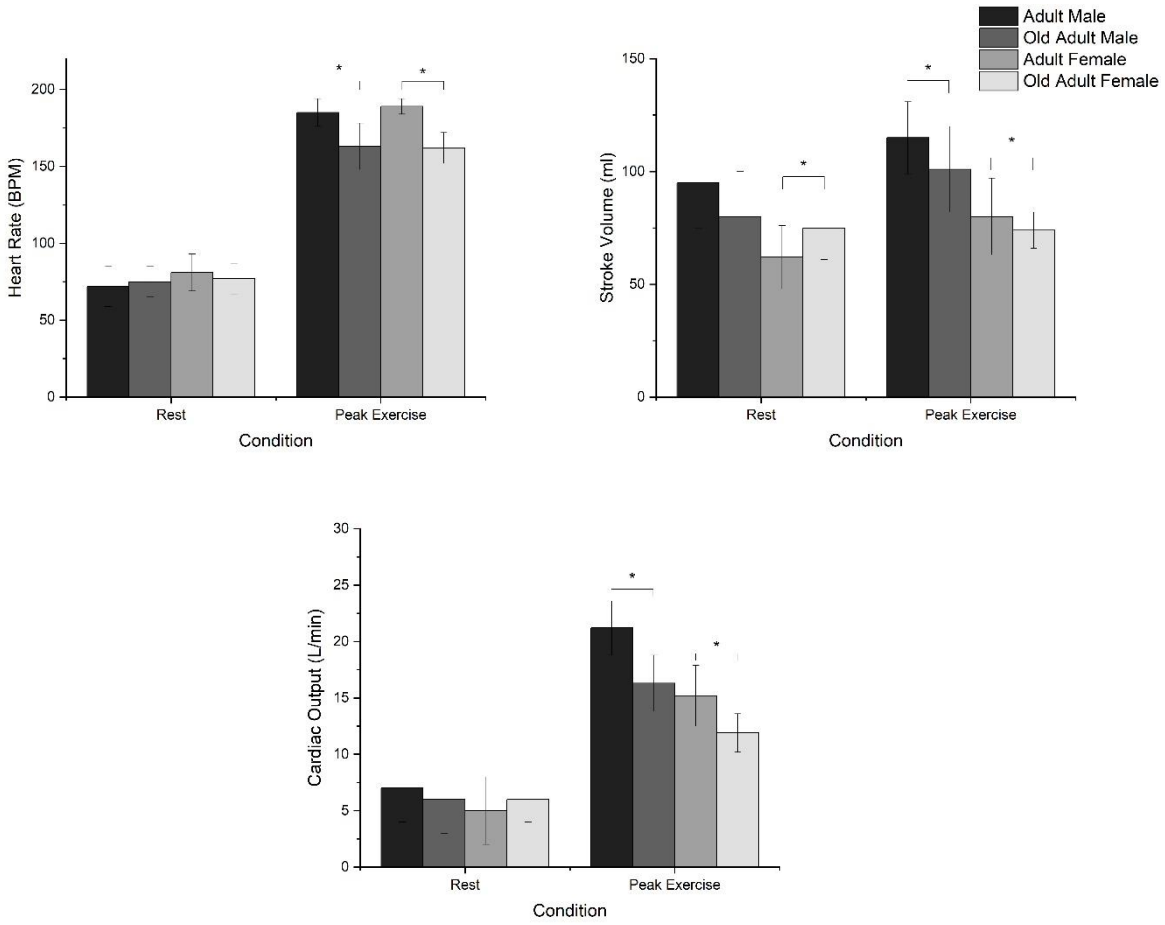


Figure 3. Heart rate (left), stroke volume (right) and cardiac output (bottom) at rest and during incremental treadmill exercise to exhaustion in young (23 – 27 ± 3y) and old (63 – 64 ± 4y) male and female populations. Figure adapted from Ogawa et al. (1992) [5, 9, 11, 13-22]. * ($p < 0.05$) indicates a significant difference between young and old humans of the same sex. Figure generated using Origin 2019b.

1.2 Adrenergic Signalling in Ventricular and Atrial Myocytes

Normal adrenergic signalling within ventricular myocytes in response to exercise is initiated through adrenaline and noradrenaline release from the adrenal medulla or the SNS from chromaffin cells and postganglionic fibres [27]. Beta1 adrenergic receptors (β_1AR) are responsible for transduction of catecholaminergic signals to enhancements in CO [33]. Catecholamines bind to β_1AR's; promoting transfer of guanosine diphosphate for guanosine triphosphate, dissociating G_s proteins into alpha (α) and β-gamma (γ) activated subunits [44]. Alpha subunits bind to adenylyl cyclase (AC), facilitating transformation of adenosine-triphosphate (ATP) to cyclic adenosine '3, '5 monophosphate (cAMP), activating cAMP dependent protein kinase A (PKA) [44]. Protein kinase A, facilitated by A kinase anchor protein complexes, phosphorylates molecules downstream [45]. Intracellular Ca^{2+} influx and Ca^{2+} induced Ca^{2+} release (CICR) is enhanced through phosphorylation of L-type Ca^{2+} channels (LTCC) and ryanodine type 2 receptors (RyR2) respectively, subsequently enhancing myocyte inotropy [46-49]. Phosphorylation of phospholamban (PLN) stimulates improved lusitropy and inotropy through alleviating inhibition of sarco/endoplasmic reticulum calcium ATPase (SERCA2a), triggering rapid Ca^{2+} uptake and enhancing sarcoplasmic reticulum (SR) loading and release [47]. Phosphorylation of troponin$_i$ (Tn_i) weakens Ca^{2+} binding between Tn_i and Tn_c, accelerating relaxation [47, 49]. Additionally, phosphorylation of specific phosphodiesterases (PDE's) modulate local cAMP levels by reducing or increasing its rate of breakdown to AMP [47, 50]. This mediates activation of PKA and enables adjustment of spatial localisation of signalling. Subsequent upregulations in myocyte Ca^{2+} cycling, triggers autophosphorylation of the Ca^{2+}/ calmodulin-dependent protein kinase (CaMKⅡ) pathway, leading to further phosphorylation of PLN, RyR2 and LTCC, enhancing the impact on CO and contractile force [27]. Adrenergic stimulation can stimulate increases in LTCC current, Ca^{2+} transients and overall myocyte contractility in the young heart by approximately 116%, 133% and 135% respectively compared to 60%, 88% and 65% in the aged heart respectively [10].

1.2.1 The Decline in Response to β_1AR Signalling

Increasing age coincides with progressive increases in sympathetic activity through amplified catecholamine spill-over from post-synaptic nerve-terminals within the heart, reduced uptake and reduced plasma clearance [27, 38]. Old adults (>65y) have been shown to exhibit circulating adrenaline concentrations 95% greater than younger adults (20-37y), whilst circulating noradrenaline concentrations are 21-40% greater [51, 52]. Old individuals also display greater catecholamine release during exercise compared to younger adults [51, 52]. One study found adults (20-37y) exhibited a 10-fold increase in adrenaline and a 7-fold increase in noradrenaline circulation, whilst old adults (>65y) displayed 11-fold increases in both adrenaline and noradrenaline circulation during maximal treadmill exercise compared to rest [52]. Elevated basal catecholamine circulation leads to chronic overstimulation of

β_1AR which is considered the main precursor to age-related changes in cardiovascular response due to desensitisation and degradation [27, 33, 38, 53, 54]. Age-related increases in sympathetic drive appear to occur as a compensatory mechanism for declining cardiac performance and efficiency as a result of mechanical, electrical and intrinsic remodelling [41, 55].

Existing research has reported reductions in β_1AR expression (11-37%) and activity (10-20 fold) in old compared to adult hearts, however initial investigations provided some contradiction, reporting unchanged β_1AR expression [27, 33, 56-60]. The differences in outcomes from initial studies likely result from dissimilar methodologies, whereby different species, genders, and age cohorts were tested, and the specific subtype of β-AR was not always specified. This stimulated greater investigation of early β_1AR signalling components. Early β_1AR signalling is mediated in part by G-protein receptor kinases (GRKs). Protein kinase A activates GRK_2 and GRK_5 which phosphorylate β_1AR, enable binding of β-arrestin proteins and prevent further G-protein coupling in a transient desensitisation process [27, 33]. This process occurs within minutes to hours, mediates further β_1AR signalling and helps control improvements in cardiovascular function during physical exertion [27, 38, 61]. Although GRKs and associated G_i proteins have been found to have a key role in the normal β_1AR desensitisation process, research suggests they have little to do with the ageing heart phenomena as studies in humans and rats demonstrate GRK and G_i activity remain unchanged in advanced age despite the increased background stimulation of β_1AR as a result of long term increases in catecholamine levels [38, 62-64]. This suggests age-related remodelling contributing to declining cardiac reserve occurs further along the β_1AR signalling pathway.

Pivotal downstream components such as AC and cAMP have been shown to be reduced in activation efficiency in response to isoproterenol (50%; >40%) in old individuals compared with responses seen in young individuals [65-67]. Reduced affinity of β_1AR for G-coupled proteins is one suggested mechanism for the downregulation of AC activity [57]. Several studies have reported aged hearts yield fewer β_1ARs in high affinity agonist binding states and thus a subsequent reduction in binding affinity compared to adult hearts, with a study in rats exhibiting as much as a 10-20-fold reduction in agonist affinity [27, 57, 58]. Furthermore, impairments in cAMP production upon stimulation have significant consequences for PKA signalling and phosphorylation of effectors further downstream in the signalling pathway [6, 42, 67, 68].

Current research shows peak LTCC current remains unchanged when increased cell size is accounted for, whilst channel inactivation slows (~137%) in old age [14-17]. Limited research has found old hearts demonstrate reduced peak LTCC current response (~50-200%) to adrenergic stimulation (Table 1) which further highlights the decline in β_1AR signalling efficiency in old age [10]. Reductions in overall LTCC function impair Ca^{2+} cycling efficiency and contribute to increased action potential duration (APD) and prolonged weaker contractions in old age [14, 15, 69-71]. One

key issue is the effect on the ratio between Ca^{2+} entry and subsequent CICR, referred to as the gain of the system. The maintenance of basal Ca^{2+} entry in aged hearts, coupled with known decreases in contractility, indicate a reduction in coupling efficiency that could potentially reduce systolic calcium transient even in the absence of changes in LTCC. This could mean during adrenergic signalling, Ca^{2+} cycling efficiency becomes vulnerable and has less ability to accommodate higher demand. It might be that concomitant age-related remodelling in ultrastructure (T-tubules) potentiate these augmentations [72]. However, this is speculation and requires further investigation.

The main age-related change in RyR2 function is an increase in channel open probability (157%) and reduced open time (~76%) at rest, possibly due to RyR2 hyperphosphorylation [13]. Such altered gating is a significant contributor to aberrant Ca^{2+} signalling in old age, evidenced through reductions in Ca^{2+} spark magnitude (~5%) and duration (~6%) alongside increased Ca^{2+} spark frequency (~91%) (Table 1) [13]. Further enhancement of RyR2 phosphorylation and thus subsequent RyR2 leak during adrenergic signalling, coupled with the reduced coupling efficiency to LTCC could cause reductions in SR load, which would further compromise calcium release. Meanwhile, the most important PLN-related change with ageing is the reduction in SERCA2a:PLN ratio (68-69%) (Table 1) [12]. This contributes to the increased Ca^{2+} transient duration and impaired relaxation in old hearts, through reduced rates of Ca^{2+} sequestration, prolonged cytosolic Ca^{2+} decay and reduced overall SR Ca^{2+} uptake magnitude (35-50%) during adrenergic signalling compared to young hearts [10, 12, 13, 20]. The reduction of cardiomyocyte relaxation in response to adrenergic stimulation in old compared to young hearts is also amplified through significant reduction in overall Tn_i expression (25-40%) and its phosphorylation by PKA (>50%) [21, 73].

In summary, investigations of components early in the signalling pathway have indicated a potential role in the loss of signalling sensitivity for β_1AR, but not GRK or G_i proteins currently in aged hearts despite their key role in transient receptor desensitisation. Studies on downstream effectors have been primarily concerned with changes in basal function, with far fewer studies evaluating changes in adrenergic response with age. Current literature suggests unfavourable age-related remodelling (Table 1) in LTCC, RyR2, SERCA2a : PLN, NCX and their overall response to adrenergic signalling generates a poor outlook for excitation contraction-coupling efficiency in the aged heart and its ability to upregulate CO during periods of greater demand. Further studies specifically investigating age-related adrenergic response in early and downstream signalling components are required. Greater attention to other effector components such as potassium currents, which also have a significant role in modulating cardiac reserve, as well as the performance of functional studies interested in ion channel fluxes and Ca^{2+} cycling at physiological frequencies, would dramatically widen understanding of true age-related remodelling at the cellular level and help identify the mechanisms underlying the subsequent deterioration at the global heart level.

Table 1. Ventricular changes with ageing. ↑ Indicates an increase, ↓ indicates a decrease, ↔ indicates no change.

Global Adaptations	Cellular Adaptations	Subcellular Adaptations
Basal SV ↓↔ [31]	APD ↑ [5, 11, 14]	LTCC Current ↑↓↔ [5, 11, 14-17]
SV Response to Stress ↓↔ [9, 74-76]	AP Amplitude ↓↔ [11, 15, 16]	LTCC Current Inactivation ↓ [5, 11, 14-17]
EDV ↓ [5, 31, 40]	Ca^{2+} Spark Magnitude ↓ [11, 13]	LTCC Current Response to Stress ↓ [10, 14]
CO and CO Range ↓ [9, 11, 29, 31, 74, 77]	Ca^{2+} Spark Duration ↓ [11, 13]	NCX Expression ↓ [11, 12]
	Ca^{2+} Spark Frequency ↑ [11, 13]	RyR2 Expression ↔ [11, 18]
	Ca^{2+} Transient Response to Stress ↓↔ [10]	RyR2 Open Probability ↑ [13]
	Contractile Response to Stress ↓↔ [5, 10, 12]	RyR2 Open Time ↓ [13]
	SR Ca^{2+} Loading ↓ [5, 11, 13, 18, 20]	SERCA2a Expression ↓↔ [5, 11, 18, 19]
		PLN Expression ↑↔ [11, 18, 20]
		SERCA2a: PLN Ratio ↓ [11, 12]
		Tn_i Expression ↓ [21, 22]

1.3 Changes in Heart Rate Response

Adrenergic signalling is responsible for modulating HR response to exercise through inducing changes in the integrated coupled clock mechanism within sino-atrial node (SAN) cells [78]. Table 2 summarises the key changes in the pacemaking mechanism with advancing age [5, 6, 65, 68, 79-83].

1.3.1 Adrenergic Signalling in the SAN – the rate modifier of peak cardiac output

In SAN cells, adrenergic stimulation triggers phosphorylation of LTCC and RyR2 by PKA, enhancing intracellular Ca^{2+} entry and SR Ca^{2+} release respectively [27, 84]. The increased cytosolic Ca^{2+} increases NCX activity improving Ca^{2+} efflux which in turn increases overall chronotropy [27, 84]. Heightened cytosolic Ca^{2+} levels also facilitate further additive downstream effector phosphorylation through greater CAMK

Ⅱ involvement [27, 84]. Finally, PKA independent cAMP directly stimulates hyperpolarisation activated cyclic nucleotide gated cation channels (HCN), elevating funny current (If) and thus AP firing, also contributing to the positive chronotropic effect [83].

Table 2. Sino atrial node changes with ageing. ↑ Indicates an increase, ↓ indicates a decrease, ↔ indicates no change.

Global Adaptations	Cellular Adaptations	Subcellular Adaptations
Basal HR ↔ [5]	APD ↑ [85, 86]	I_f Current Density ↓ [82]
Intrinsic HR ↓ [80, 82, 85-87]	Intrinsic AP Firing ↓ [68, 82]	I_f Current Response to Stress ↔ [82]
Maximum HR ↓ [5, 9, 74, 75, 82, 87]	Maximum AP Firing ↓ [68, 82]	LTCC Current Response to Stress ↔ [82]
HR Response to Stress ↓ [9, 74-77, 87, 88]	Ca^{2+} Transient Magnitude ↓ [68]	T-Type Ca^{2+} Channel Current Response to Stress ↔ [82]
	Ca^{2+} Transient Duration ↑ [68]	RyR2 Expression ↓ [68, 86, 89]
	CICR ↓ [68]	SERCA2a Expression ↓↑ [68]
		HCN_2 and HCN_4 Expression ↓ [81, 89]
		$Connexin_{43}$ Expression ↓ [79, 89]

1.3.2 Changes in the coupled clock mechanism with ageing

Advancing age is associated with reduced intrinsic HR as a result of declining SAN function [5, 80]. However, resting HR remains unchanged due to increased SNS input and elevated catecholamine circulation [87]. Age-related reductions in connexin43 (~94%) [79] alongside increased type-1 collagen production and crosslinking, may provide a substrate for conduction impairments and constrain the ability to attain a high HR [90, 91]. Also, age-related SAN hypertrophy [82] may increase conduction time due to greater distances travelled by impulses, whilst the loss of overall SAN cells may cause a decline in electrical drive due to electrotonic effects from the surrounding tissue that the SAN has to drive [82]. Age-related SAN remodelling also includes reductions in LTCC expression (20-45%, 1 and 18 month vs 38 month guinea pigs) [92] and I_f density (34-52%, 2-3 vs 21-24 and 28+month mice) as a result of decreased HCN2 (~51%) and HCN4 (~61%) expression (rats; 30 vs 1 month) [81, 82] [82]. Such changes in membrane clock components contribute

to reduced AP amplitude, increased APD and reduced ability to produce high HR [68, 82]. Age-related changes in Ca^{2+} clock involve remodelling of Ca^{2+} transporters and release units [6]. Reduced SERCA2a (~30%), PLN and RyR2 (~90%) expression have been reported in SAN cells in old compared to adult hearts [68]. Such changes facilitate age-related reductions in Ca^{2+} transient amplitude (23%) and CICR (38%) and elevations in Ca^{2+} transient duration (57%) (mouse, 2-4 vs 20-27months) [68]. Existing research investigating the interaction of the membrane clock and adrenergic stimulus has found reductions in peak I_f density (36-57%) during adrenergic stimulation in aged mice (21-24 and 28+ vs 2-3months) [82]. Similar findings have been observed in aged rats [54]. Age-related remodelling in the SAN appears to support the constriction of HR range through alterations in adrenergic signalling modulation and through the impairment of components involved in the β_1AR signalling mechanism according to research [42, 64-68]. Further studies investigating age and adrenergic signalling interaction on Ca^{2+} cycling are required.

1.4 Effects of exercise training on adrenergic response

Despite the considerable range of changes in myocardial structure and function, generally considered deleterious, associated with advanced age, the prognosis may not necessarily be so bleak. Pharmacological and non-pharmacological interventions have been shown to aid restoration of some components which are key for adrenergic signalling and are associated with improvements in cardiac reserve ranging from improvements of 11% to almost complete restoration [6, 75, 93-102]. Non-pharmacological interventions such as exercise may be especially beneficial due to the widely-known associated health benefits and much lower probability of deleterious side effects [103-105].

1.4.1 Exercise Training and the Adult Heart

In normal healthy adult hearts, exercise training generally causes a shift toward bradycardic phenotypes and expands cardiac reserve through the widening of HR range as a result of lower resting HR and also by better preserving or improving the efficiency of adrenergic signalling [94, 95, 106-108]. Exercise training in adult rats has been found to prolong ventricular APD (14-69%) [107, 109], reduce the transmural gradient of AP duration (37-99%) [109] and prolong Ca^{2+} transient duration (10-12%) [107]. Reductions in APD (12-18%) in response to high activation rates (10Hz; equivalent to very heavy exercising HR in rats) have also been found with training [107]. Exercise-induced prolongations in APD are considered a result of alterations in repolarising K^+ currents as well as a shift in adrenergic signalling efficiency [107, 109, 110]. Recent research has found exercise training increases ATP-sensitive potassium current (KATP) (50-70%) at high activation rates (10Hz) and reduces slowly activating delayed rectifier potassium channel (Ik_s) current at rest

(13-23%) and during adrenergic stimulation (11-34%) [107, 110, 111]. Meanwhile, resistance training in adult rats has been found to elevate SERCA2a expression (~19%) and subsequently improve myocyte relaxation (~8% reduction in time to half myocyte relaxation) and contraction (~4% reduction in time to myocyte contraction) [112]. The changes described above point to improvements in adrenergic signal transduction, mechanical efficiency, AP repolarisation reserve and overall cardiac reserve. This cellular remodelling is typically reflected at the global level through lower resting HR, increased SV and thus CO and a far greater reserve for upregulating cardiac function during stress.

1.4.2 Exercise Training and the Aged Heart

Existing literature suggests a period of chronic exercise training, normally aerobically based, leads to improved early diastolic filling (~10-30%) and enhanced contractility (~30% increase in systolic reserve; ~19% increase in peak CO; ~22% increase in peak SV) during exercise in old adults, directly through mediations in β_1-AR signalling amongst other mechanisms [6, 93]. Exercise training in aged rats has been shown to improve AC activity and cAMP production response to adrenergic stimulation [6, 96, 97]. Expression of β_1AR either remains the same or undergoes partial restoration after a period of exercise training [6, 96, 97]. Similar changes are seen in SERCA2a expression in old hearts with training, meanwhile RyR2, PLN and NCX largely remain unaltered [6, 101, 113-115]. Whereas heterogenous changes were seen after exercise training in aged compared to younger adult mice Ca^{2+} channels [115]. Exercise training has been found to influence LTCC expression through restoration of Ca_v 1.3 without changes in Ca_v 1.2 [115]. At the global level, research suggests exercise training lacks effect on peak HR despite reported restorations in CO and thus relies on improvements related to SV as suggested in previous research [93, 102]. However, whether improvements in contractility or diastolic filling provide greater CO improvements is unclear. Research suggests lifelong or extensive periods of exercise training yields superior diastolic function when compared to control groups, however this does not mean immunity to age-related decline [6, 116-118]. Research is slightly less unanimous in regards to the benefit of shorter bouts of exercise training on diastolic function in relation to ageing [6, 116, 117]. Meanwhile, exercise training improves systolic reserve whilst basal function remains largely similar with ageing [6, 117, 118]. It could be that changes favouring diastolic filling are largely responsible since the old heart is reliant on the Frank-Starling mechanism for upregulating CO, or rejuvenations in contractility may restore SNS modulation and thus a more youthful phenotype. Restoring CO in any capacity in old individuals is vital for improving exercise tolerance and quality of life.

1.5 Key potential future studies

Future research must focus on lesser understood changes in HR and SV interactions occurring with age in response to adrenergic signalling and attempt to map the rate of ageing decrements. In a similar vein, investigating the changes in β_1AR expression alongside the content of other components involved in the β_1AR signalling pathway may help identify the point at which increased sympathetic activity begins to become detrimental to cardiovascular function. Such information would benefit research interested in implementing therapeutic strategies, potentially highlighting the optimal point of intervention to achieve maximal benefit. Previous research has exposed vast inherent heterogeneity in the heart, however, the way in which age-related remodelling effects this heterogeneity, particularly in regard to key components of the adrenergic signalling mechanism is unknown and warrants much further investigation. Moreover, research focusing directly on aspects linked to cardiac repolarisation is limited. Given the well-known control β_1AR signalling has on the modulation of repolarisation, further investigation of ion channels as well as other factors involved in the control of repolarisation both at rest and during response to stress in respect to the ageing phenomenon may help elucidate the foundational remodelling of cardiac excitation that leads to the impairment of contractility and constriction of cardiac reserve.

Further studies involving exercise training as a cardio-protective strategy are also required. Greater focus on the remodelling of cardiac excitation may help to understand the differential effects of exercise training on APD and β_1AR sensitivity. As mentioned previously, a shift towards a bradycardic phenotype coupled with seemingly greater β_1AR signalling efficiency and subsequent repolarisation reserve, evidenced by improved function and a reduction in β_1AR sensitivity (rightward shift) alongside APD prolongation, may be observed in adult hearts with exercise training, however in the aged heart studies so far point to a beneficial potential re-sensitisation of β_1AR signalling with exercise training leading to the widening of systolic reserve. The mechanism which this specifically occurs by and the full range of β_1AR effector component changes are yet to be studied in the aged heart. Additional studies aimed at assessing functional and structural changes may help to highlight the mechanisms underlying the potential differences in training-induced remodelling of β_1AR components and subsequent adrenergic response between adult and old hearts. The influences of life-long training and extreme exercise participation may also make for interesting studies due to the possibility of additive cardioprotection or conversely detrimental remodelling.

Finally, a great deal of the literature has utilised animal models and whilst they are robust and proven models that provide vital insight for extrapolation to humans, differences exist in expression levels and impact of various components covered in this review and thus certain remodelling may present as entirely different or have varied levels of importance depending on the species in question. Therefore, where possible, increasing human investigations will enable key reference points for structural components and functional changes to be developed.

2.0 Conclusion

In summary, ageing impacts cardiac and overall physical function and has implications for mobility and morbidity. Adrenergic signalling in the ageing heart represents a key area of research providing cellular explanations for age-related losses in cardiac reserve. Despite extensive investigation of β_1AR signalling changes there is more to uncover, and many mixed findings exist. Exercise presents a non-pharmacological intervention that may aid restoration of some downregulated mechanisms associated with ageing and thus cardiac reserve. Findings from exercise training studies so far show promise in restoring various components involved in the adrenergic signalling pathway – depleted in old age – as well as global function to some level [95, 99, 100, 108], however far greater research is required to fully map the potential of exercise as a method of rejuvenating or blunting the declining ability to maintain CO during physical activity in old individuals.

3.0 Author contributions

LH and ML conceived the topic of the review. LH drafted the review. ML and LH edited and revised the manuscript. All authors approved the final version.

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5.0 Conflict of interest

No conflicts of interest are declared by the authors.

6.0 References

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