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The Role of Exercise in Cardiac Aging: From Physiology to Molecular Mechanisms

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Abstract

Aging induces structural and functional changes in the heart that are associated with increased risk of cardiovascular disease and impaired functional capacity in the elderly. Exercise is a diagnostic and therapeutic tool, with the potential to provide insights into clinical diagnosis and prognosis, as well as the molecular mechanisms by which aging influences cardiac physiology and function. In this review, we first provide an overview of how aging impacts the cardiac response to exercise and the implications this has for functional capacity in older adults. We then review the underlying molecular mechanisms by which cardiac aging contributes to exercise intolerance, and conversely how exercise training can potentially modulate aging phenotypes in the heart. Finally, we highlight the potential use of these exercise models to complement models of disease in efforts to uncover new therapeutic targets to prevent or treat heart disease in the aging population.

Keywords

exercise; aging; cardiovascular disease

Introduction

Improvements in public health over the past century have led to dramatic increases in life expectancy. By 2030, adults over the age of 65 will account for nearly 20% of the general population in the US[1]. Moreover, the oldest demographic groups, consisting of individuals 85 years or older, now represent the fasting growing segment in the US, and are estimated to increase by more than 230% by 2050[1]. Thus understanding the factors limiting health and quality of life in the elderly will be increasingly important over the coming years. Among these factors, cardiovascular disease represents the leading cause of mortality in the elderly, accounting for nearly 40% of all deaths[1, 2]. Heart failure (HF), in particular, is reaching

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DISCLOSURES

None.

epidemic proportions with approximately 88% of HF deaths and greater than 75% of all HF hospitalizations in the US now occurring in adults 65 years or older[3].

While advanced age is considered a major independent risk factor for HF, the mechanisms by which aging predisposes older adults to HF are not completely understood. The cumulative impact of repeated insults and injuries (i.e. myocardial infarctions, hypertension) to the heart throughout its lifetime is undoubtedly an important contributor to maladaptive myocardial remodeling and the development of HF in the elderly. However, there are also factors intrinsic to cardiac aging, occurring at a cellular and molecular level, which may impair the overall function of the heart as it approaches senescence[4–6].

While it can be difficult to completely separate extrinsic from intrinsic factors in cardiac aging given the interactions between aging, disease, and environment, genome-wide transcriptome analyses of whole hearts and isolated cardiomyocytes from healthy young and old mice have provided some insights into the molecular mechanisms of aging in the heart. Specific transcriptional alterations in pathways related to stress response, mitochondrial function, fatty acid metabolism, contractility, hypertrophy, inflammation, and extracellular matrix production have been identified as key molecular phenotypes of cardiac aging, which interestingly parallel many of the transcriptional changes that occur in the failing heart[7, 8]. Although the aged heart is generally capable of meeting the basal energy requirements of the body, its performance under physiologic and/or pathologic stress can be significantly impaired, which can lead to exercise intolerance and dyspnea, the primary symptoms of HF. Thus, defining the mechanisms by which aging affects the heart's ability to respond to stressful stimuli becomes integral to understanding the role of aging in HF pathophysiology.

Exercise, as an inducible form of physiologic stress, represents a powerful tool in cardiac aging research for this very reason. Exercise physiology has provided a wealth of knowledge into how age-related changes in cardiac structure and function translate to decreased exercise capacity[9, 10], a strong determinant of HF prognosis, quality of life, and mortality in the elderly[11, 12]. Furthermore, exercise-based studies in aged animal models are now beginning to identify the molecular mechanisms of cardiac aging that contribute to exercise intolerance, and intriguingly suggest that exercise, as a therapeutic intervention, can potentially mitigate or reverse some aspects of the aging process in the heart.

Both aging and exercise are complex systemic processes that influence nearly every facet of the cardiovascular system. Here we primarily focus on the role of exercise in the aged heart, with an emphasis on cardiomyocyte biology. We first provide an overview of how aging impacts the cardiac response to acute exercise and the implications this has on declining functional capacity in the elderly. We then review the literature on exercise in aged animals, highlighting the major molecular mechanisms by which cardiomyocyte aging is thought to contribute to exercise intolerance and how exercise training potentially modulates these properties in the aged heart. Finally, given the parallels in exercise and cardiac phenotypes observed in advanced age and HF, we discuss the potential implications of these findings in the context of the growing HF epidemic in the aging population.

Effects of aging on the cardiac response to exercise

Exercise exerts a physiologic stress on the body, requiring a coordinated response by the cardiovascular, pulmonary, and nervous systems to increase blood flow and oxygen supply to the working skeletal muscle. At rest, muscle receives approximately 20% of the total blood flow, but during exercise, this can increase to over 80%[13]. Thus, impairments in any of these systems can lead to significant decreases in peak cardiac output (CO) and overall exercise capacity.

The heart's contributions to augmenting CO in response to the increased metabolic demands of exercise have been well characterized, and essentially depend on dynamic regulation of two physiological parameters, heart rate (HR) and stroke volume (SV). In healthy young adults, exercise-induced adrenergic stimulation rapidly increases both HR and SV, with the latter being primarily enhanced by increased myocardial contractility and decreased peripheral vascular resistance. SV increases proportionally with exercise intensity until about 40–50% of maximal capacity, after which it tends to plateau and additional augmentation of CO is driven by a further increase in HR[14].

While older adults are still capable of augmenting their CO in response to exercise, the relative increase is typically diminished compared to their younger counterparts. Reduced maximal HR, also known as chronotropic incompetence, is a major contributor to the diminished cardiac response to exercise in older adults. Normal aging results in a progressive decline in maximal HR by approximately 0.7 beats/min/year[15]. Although the mechanisms for chronotropic incompetence are not completely understood, degenerative changes in the conduction system along with impaired autonomic regulation likely play central roles[16]. Importantly, age-related decrease in peak HR strongly correlates with diminished exercise capacity, and is an independent predictor of adverse cardiovascular events and mortality[17, 18].

The impact of aging on SV augmentation with exercise is not as clear with varying degrees of SV reserve reported in different studies[19–22]. In general, aged hearts are still capable of increasing SV in response to exercise, albeit at levels insufficient to offset the reduction in maximum HR. Interestingly, the mechanism by which the heart augments SV with exercise changes with age. While enhanced myocardial contractility is the primary means of increasing SV in young hearts, exercise increases SV in aged hearts mainly through increased end-diastolic volumes with minimal changes in contractility[10].

Overall, normal aging significantly diminishes both the chronotropic and inotropic responses of the heart to exercise (Table 1). Clinically, this phenomenon is referred to as impaired cardiac reserve, which is the inability of the heart to adequately augment CO to meet the increased demands of physiologic stress, whether induced by exercise or pharmacologically (i.e. dobutamine). In conjunction with age-associated alterations in peripheral mechanisms of oxygen extraction and utilization in skeletal muscle[19, 21, 23, 24], inadequate oxygen delivery from impaired cardiac reserve is a major contributor to decreased functional capacity in the elderly, especially those with HF[19, 25,26]. Maximum oxygen consumption (VO2max), which is the maximal rate the body can consume oxygen during incremental

exercise, is an established metric of exercise capacity. With normal aging, VO2max declines by approximately 10% per decade in healthy ambulatory individuals[22], but this decline notably accelerates at ages above 70 years and in HF[27], suggesting that mechanisms that lead to impaired cardiac reserve in aging may be particularly relevant to the increased HF risk seen with advanced age.

Rodent models of cardiac aging and exercise intolerance

While human studies have provided valuable insights into how aging influences cardiovascular physiology and functional capacity, limited access to tissue has been a major obstacle to elucidating the molecular mechanisms of aging that impair cardiac reserve. In this regard, rodent models have been particularly useful because of their relatively short lifespans, genetic manipulability, and similar cardiac aging phenotypes to humans[5]. Based on survival data, mice and rats, around 24 months of age, are typically used to model older humans[28], although even this pre-specified age cutoff must be carefully considered given the wide variation in lifespan across strains[29]. In general, rodent hearts at this age exhibit similar structural and functional phenotypes to older human hearts, including impaired contractile reserves, diastolic dysfunction, hypertrophy, fibrosis, and vascular stiffening[30].

Importantly, despite having increased basal metabolic requirements and higher resting HR, rodents demonstrate comparable exercise physiology to humans, which can be reliably assessed when careful attention is paid to exercise testing conditions[31]. Continuous invasive hemodynamic monitoring in adult (3–4 month) mice has shown that they augment CO by approximately 2-fold (9.6±0.6ml/min at rest to 18.9±0.9ml/min at peak exercise) in response to acute exercise[32]. The increased CO is primarily derived from a marked increase in HR (489±18bpm at rest to 798±9bpm at peak exercise) and modest SV augmentation. Moreover, similar to humans, as rodents age, exercise capacity progressively declines. VO2max decreases by approximately 28% in healthy 24-month-old C57BL/6J mice, compared with 12-month-old mice[33]. A similar pattern is seen in Fischer 344 × Brown Norway F1 (F344/BNF1) rats, which display 10% and 33% decreases in VO2max at 24 and 35 months, respectively, compared with 12-month-old rats[34].

Even in rodents defining intrinsic factors of aging that influence cardiac reserve and exercise capacity is difficult. Based on the central role of the autonomic nervous system on cardiac exercise response, a substantial amount of research has focused on autonomic dysregulation in the aged heart, as described in more detail below. Recent studies by Wisloff and colleagues have used a breeding selection strategy in rats based on exercise capacity (referred to as the aerobic hypothesis)[35]. From 1996–2011, selective breeding of a genetically heterogeneous N:NIH rat stock (28 generations, n=11,606 rats) eventually generated two distinct lines that differed in maximal running capacity by approximately 7-fold. Comparative analyses of hearts and isolated cardiomyocytes from aged rats with low and high intrinsic running capacities subsequently identified mitochondrial dysfunction[36], abnormal calcium (Ca^{2+}) handling[37], increased hypertrophy,[38] and microvascular dysfunction as key molecular phenotypes in the heart associated with exercise intolerance in aging (Figure 1).

We will now explore in more detail how these features of cardiomyocyte aging impair the aged heart's response to acute exercise, and how exercise interventions potentially modulate these aging phenotypes. While adaptive changes in the vasculature are important in both aging and exercise physiology, a complete discussion of this topic is beyond the scope of this review, and we refer the interested reader to the following references as an introduction to this topic[4, 39].

Exercise and autonomic regulation of the aged heart

The heart's response to acute exercise is largely regulated by the autonomic nervous system. During exercise, increased sympathetic tone augments both HR and contractility, while concomitant parasympathetic withdrawal further enhances the chronotropic response. As the heart ages, however, its responsiveness to autonomic stimuli significantly diminishes. Evidence in humans and animals suggests that these age-associated changes in cardiac autonomic regulation play important roles in declining cardiac reserve and exercise capacity seen with aging[40].

Age-associated autonomic dysregulation and impaired cardiac reserve

Sympathetic dysregulation in the aged heart is primarily derived through a process known as β-adrenergic receptor (β-AR) desensitization. With normal aging, circulating norepinephrine levels increase by 10–15% per decade[41]. In the heart, local norepinephrine levels also increase with age due to diminished reuptake and increased tissue spillover[42]. Greater β-AR occupancy by catecholamines triggers a compensatory mechanism in aged cardiomyocytes that results in desensitization of the post-synaptic machinery, and ultimately blunted intracellular Ca^{2+} transients and impaired inotropic and chronotropic responses to adrenergic stimulation[43, 44].

The mechanisms underlying β-AR desensitization in the aged heart are complex, with alterations occurring at multiple levels along the β-AR/G-protein/adenylyl cyclase (AC) pathway. Reduced β-AR density has been reported in older human[45] and rat[46] hearts, implying that at least part of this process is modulated at the receptor level. Additionally, numerous alterations in downstream G-proteins and AC catalytic units have been identified in the aging myocardium. Evidence from senescent rats and guinea pigs has suggested that cardiac Gi protein levels and pertussin-toxin (PTX)-mediated Gi ribosylation increase with age[47, 48]. However, other studies in humans and rats have demonstrated that Gi levels are unchanged in aged cardiomyocytes, and furthermore, their reduced contractile response to adrenergic stimulation cannot be rescued by inhibiting Gi with PTX[45, 46]. Rather, these studies argue that age-related β-AR desensitization is primarily mediated through diminished β-AR density, reduced Gs, and impairments in AC activity.

While the mechanisms responsible for the age-dependent decline in cardiac β-AR responsiveness are not completely understood, it is clear that this process results in impaired cAMP production and protein kinase A (PKA) activity, which are necessary for augmenting intracellular Ca^{2+} transients and enhancing cardiac contractility during exercise[49, 50]. Impaired cAMP/PKA signaling may in part be due to persistent activation of Ca^{2+}/calmodulin kinase II (CaMKII), another downstream effector of β-AR signaling.

Interestingly, while constitutive β-AR stimulation leads to down-regulation of PKA signaling, CaMKII activity remains high. Persistent CaMKII activity can desensitize cardiomyocytes to PKA signaling[51, 52], and moreover, has been linked to apoptosis and pathologic hypertrophy in failing cardiomyocytes[53, 54].

Alterations in parasympathetic control of the aged heart have not been as extensively studied. In rats, the data has been conflicting with age-associated changes in the density and function of cardiac muscarinic M2 receptors reported to be unchanged, decreased, or increased[55]. In humans, the density of cardiac M2 receptors appears to decline with age.[56] Moreover, aged human hearts demonstrate impaired chronotropic responses to acute parasympathetic withdrawal, suggesting that impaired muscarinic receptor activity may contribute to the blunted HR response to exercise in the elderly[57, 58].

Given that exercise primarily mediates its effects on the heart through dynamic regulation of the autonomic system, it seems likely that these age-associated changes in β-adrenergic and muscarinic receptor pathways play important roles in the impaired cardiac response to exercise in older adults. Notably, down-regulation of β-AR density and activity is seen in failing hearts from younger adults, who exhibit similar declines in cardiac reserve and exercise capacity[51]. Likewise, acute β-AR blockade in healthy young adults recapitulates the aging cardiac response to exercise with blunted maximal HR, decreased myocardial contractility, and increased end-diastolic volumes[59]. Collectively, these data support an important functional role for altered sympathetic and parasympathetic signaling in cardiac phenotypes associated with aging.

Effects of exercise training on β-AR desensitization in the aged heart

There is modest evidence in older humans and rats indicating that exercise training can reverse, or “resensitize”, the aged heart to adrenergic stimuli and improve cardiac reserve[60]. Nine months of aerobic exercise in previously sedentary, older men (~65 years) increased exercise capacity by 28%, in addition to improving contractility and early diastolic filling rates at peak exercise[61]. Importantly, these exercise-induced changes were completely abrogated by acute β1-receptor blockade, suggesting that the observed effects of training on the aged heart were likely mediated through direct modulation of β-AR signaling.

Similar findings have been demonstrated in aged rats. While 12 weeks of moderate intensity treadmill running in 28-month-old Sprague-Dawley rats did not change β-AR density, it significantly decreased downstream Gi activity and enhanced isoprenaline-stimulated AC activity[47]. A follow-up study, in which 24-month-old Wistar-Kyoto rats were run at 70–80% VO2max for 12 weeks, demonstrated that higher intensity training increased β-AR density and AC activity in aged hearts, resulting in enhanced responsiveness to adrenergic stimulation and restoration of inotropic, lusitropic, and chronotropic properties[62].

While numerous differences in experimental conditions are present between these two studies (Table 2), it is intriguing to hypothesize that exercise “dose” or subject age may have influenced the varying effects of training on β-AR density in the aged hearts. Indeed, data from humans and rodents has suggested that a threshold “dose” of exercise may be necessary to generate significant changes in the heart[63–65]. In adult rats, direct comparison

of moderate (65–70% VO2max) and high (85–90% VO2max) intensity treadmill running demonstrated that higher intensity training not only improved exercise capacity to a greater extent, but it also correlated with a dose-dependent increase in cardiomyocyte hypertrophy, contractility/relaxation, and Ca^{2+} handling[65]. Furthermore, age also appears to play a role exercise-induced modulation of β-AR signaling. In young animals, aerobic training decreases cardiac Gi activity, but generally has little to no effect on β-adrenergic/muscarinic receptor densities or downstream AC activity[47]. In fact, direct comparison of high intensity (75% VO2max) treadmill running in young (3 month) versus old (23 month) F344 rats showed that adrenergic-stimulated AC activity was actually decreased in young rats, while up-regulated in older rats[66].

Exercise and Ca^{2+} regulation in the aged heart

Calcium handling is regulated by β-adrenergic signaling in cardiomyocytes and plays a central role in modulating cellular contraction and relaxation through excitation-contraction (EC) coupling. Numerous age-related changes in key components of cardiomyocyte Ca^{2+} handling, however, impair both the systolic and diastolic properties of the aged heart.

Age-associated impairments in Ca^{2+} handling

In order to augment myocardial contractility, relaxation, and overall cardiac performance during acute exercise, EC coupling must be quickly modified within individual cardiomyocytes to increase the rate of rise and decay of intracellular Ca^{2+} transients. In young cardiomyocytes, peak contractions and Ca^{2+} transients increase and decay more rapidly at higher stimulation frequencies[67, 68]. While aged cardiomyocytes display similar peak contractions at slow stimulation rates, they produce much smaller increases in peak Ca^{2+} transients and cell shortening at more rapid pacing rates[68]. Additionally, rates of Ca^{2+} decay are significantly prolonged in aged cardiomyocytes compared with younger cells. At an organ level, these findings translate to preserved systolic function under resting conditions, but prolonged myocardial relaxation (a hallmark of age-related diastolic dysfunction) and impairments in the ability to augment contractility at the faster HR elicited by exercise.

Impairments in intracellular Ca^{2+} handling in aged cardiomyocytes are largely derived from age-associated changes in the proteins involved in EC coupling. Decreased levels of sarcoplasmic reticulum Ca^{2+}–ATPase (SERCA2a) are thought to be a primary mechanism for the prolonged Ca^{2+} transients in the aged myocardium[69–72]. Cardiac SERCA2a gene transfer in senescent rats restores diastolic function back to youthful levels[73]. Additionally, aged-associated alterations in SERCA2a regulatory proteins, including phospholamban (PLB)[74], PKA[49] , and CaMKII[75] have also been documented in the aged heart, with the direction of these changes expected to decrease SERCA2a activity and prolong Ca^{2+} transients. Evidence of age-related changes in other proteins involved in cardiomyocyte Ca^{2+} regulation, including the Na^{+}/Ca^{2+} exchanger (NCX), ryanodine receptors (RyR), and calsequestrin have not been as consistent or would not necessarily be expected to significantly alter Ca^{2+} transients[76].

Effects of exercise training on Ca^{2+} handling in the aged heart

Whether exercise training can improve intracellular Ca^{2+} cycling and performance of the aged heart is not entirely clear. In healthy young rodents, aerobic exercise training leads to faster rise and decay rates of Ca^{2+} transients in cardiomyocytes, and subsequent improvements in systolic and diastolic function[65, 77]. The mechanisms for these exercise-induced alterations in Ca^{2+} cycling in young hearts are potentially mediated through more effective coupling of L-type Ca^{2+} channels and RyR receptors, increased SERCA2a and NCX expression, enhanced SERCA2a function via transient CaMKII activation or PLB inhibition, and/or improved myofilament Ca^{2+} sensitivity[77–79].

Aerobic training studies in aged rodents suggest that these benefits are not limited to young animals, and appear to be primarily driven by enhanced SERCA2a expression. Eight to ten weeks of treadmill running increases SERCA2a levels in the hearts of 24-month-old F344 rats[80]. Furthermore, isolated cardiomyocytes from these rats display improved Ca^{2+} cycling and more rapid contractility and relaxation times that are associated with increased SERCA2a expression[81]. Twelve weeks of high intensity (70–85% VO2max) treadmill running in young (6 month) and old (24 month) F344/BNF1 rats also largely reverses impairments in early diastolic filling rates in the older cohort. This effect is not seen in younger animals, suggesting that exercise has specific modulatory effects on age-related impairments in active myocardial relaxation, presumably through improved Ca^{2+} cycling[82]. Swimming old (21 month) Wistar rats also induces similar increases in cardiac SERCA2a expression[83]. However, other studies have demonstrated that SERCA2a and other related Ca^{2+} channels (i.e. RyR, NCX) are not increased in aged rodents by aerobic training[84, 85]. Notably these latter studies were done at significantly lower exercise intensities (Table 2), emphasizing the importance of evaluating exercise protocols in interpreting results of training.

Exercise and age-related cardiac hypertrophy

Cardiac hypertrophy, a composite of cardiomyocyte growth and increased extracellular matrix deposition, is a hallmark feature of cardiac aging[86, 87], and is associated with diastolic dysfunction, HF, and mortality in the elderly[88, 89]. While age-related vascular remodeling undoubtedly influences cardiomyocyte growth in the aged heart, both human and animal studies indicate that mechanisms independent of changing hemodynamics also contribute[86, 90]. Cardiomyocyte hypertrophy in the aged heart may in part be a compensatory reaction to a cumulative loss of myocytes with normal aging[91, 92]. Declining regenerative potential in the aged heart[93] appears insufficient to counterbalance this loss. While age-related hypertrophy minimizes myocardial wall stress and can help maintain overall cardiac function, at a cellular level, it can also be viewed as a marker of increased stress and altered homeostasis, and is generally felt to be a pathologic process associated with increased apoptosis, impaired Ca^{2+} regulation, and defective macroautophagy[94–96].

Mechanisms of age-related cardiac hypertrophy

Many of the molecular mechanisms underlying cardiomyocyte hypertrophy in the aged heart appear similar to the intracellular signaling pathways that drive pathologic growth in

hypertension and HF[97]. Chronically activated neurohormonal systems, including the adrenergic, endothelin, and renin-angiotensin-aldosterone systems, along with increased workload and biomechanical strain on the remaining cardiomyocytes stimulate numerous growth pathways, including the mitogen-activated protein kinases (MAPK), histone deacetylases (HDAC), calcineurin/nuclear factor of activated T cells (NFAT), and insulin-like growth factor-I (IGF-I)-phosphatidylinositol 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathways. For a detailed discussion of these growth pathways in the heart, we refer the interested reader to an excellent review by Heineke and Molkentin[98].

While many of these signaling pathways, including p38, c-jun N-terminal kinase, extracellular signal-regulated kinase-1/2 (ERK-1/2), calcineurin/NFAT, and PI3K/Akt/mTOR, are up-regulated in aging rodent hearts[99, 100], whether they are directly regulated by aging and what the relative contribution of each of these pathways in age-related cardiac hypertrophy is not clearly defined. Cardiac specific gain- and loss-of-function studies have provided some supportive evidence for a direct role of neurohormonal pathways in age-related cardiomyocyte hypertrophy. Genetic ablation of cardiomyocyte endothelin-A receptors attenuates age-associated cardiomyocyte hypertrophy[101], while cardiomyocyte-specific β-AR1[102] or angiotensin II[97] overexpression induces significant myocyte growth in aging hearts. Similarly, cardiac specific suppression of PI3K[103], as well as systemic mTOR inhibition with rapamycin[104], reverses hypertrophy and lipofuscin accumulation in aged murine hearts. The role of HDACs, particularly NAD-dependent sirtuins, have recently emerged as important regulators of age-related cardiac hypertrophy and longevity, and will be discussed in detail later in this review.

Most recently, heterochronic parabiosis studies in mice have suggested that there may in fact be age-specific mechanisms of cardiomyocyte hypertrophy. Using a novel aptamer-based proteomics screen in this mouse model, Loffredo and colleagues found that systemic levels of growth differentiation factor-11 (GDF11), a secreted member of the TGF-β superfamily, decline with normal aging[105]. Interestingly, restoration of GDF11 levels in 24-month-old C57BL/6 mice reversed age-related cardiomyocyte hypertrophy and improved SERCA2a expression in the heart. Recent work by Smith and colleagues, however, found that GDF11 therapy did not alter cardiomyocyte hypertrophy in old C57BL/6 mice and moreover did not affect cardiac function[106]. The reason for these differing results is currently unclear as similar GDF11 interventions and aged murine strains were used in both studies.

Interestingly, GDF11 shares many structural and functional properties with myostatin, another TGF-β superfamily member (also known as GDF8). Aging studies in germline myostatin knockout mice have suggested that while systemic myostatin inhibition induces modest cardiac hypertrophy in senescent mice, it also decreases myocardial fibrosis and improves systolic function[107]. Indeed, both hearts and isolated cardiomyocytes from aged germline knockouts demonstrate improved β-adrenergic responsiveness, Ca^{2+} handling, and enhanced contractility to sympathetic stimulation[107–109]. Taken together, these data suggest that myostatin inhibition may induce physiologic, as opposed to pathologic hypertrophy, in the aged heart. As further evidence, chronic pressure overload through transverse aortic constriction (TAC) does not alter the hypertrophic response in cardiac specific myostatin knockout mice[110] and likewise, GDF11 therapy has no effect on TAC-induced pathologic

hypertrophy[105]. Recent work by Egerman and colleagues have highlighted the difficulty in distinguishing between myostatin and GDF11 in some of the currently available assays[111], emphasizing the need for further study to understand the potentially interrelated roles of these closely related peptides in cardiac aging.

Mechanisms of exercise-induced cardiac hypertrophy

Similar to aging and HF, exercise can induce a dramatic increase in cardiac mass that is predominantly mediated by cardiomyocyte growth[112, 113]. However, unlike age-related cardiac hypertrophy exercise elicits a more “physiologic” growth that is felt to be cardioprotective. Not only are the outcomes of these two kinds of cardiac growth different, but the underlying molecular mechanisms are also largely distinct[114].

Exercise-induced hypertrophy is mediated largely through increased IGF-1 signaling in the heart[115]. Cardiac-specific IGF-1 receptor knockout mice do not develop cardiac hypertrophy in response to exercise, suggesting that initial IGF-1 signaling is necessary for exercise-induced cardiac growth[116]. Stimulated IGF-1 receptors subsequently activate PI3K, a family of heterodimeric kinases that regulate membrane lipid phosphoinositides. Cardiac-specific expression of a dominant negative PI3K 110alpha isoform also inhibits exercise-induced cardiac growth[117, 118]. Similarly, germline deletion of the PI3K–effector, Akt1, abolishes exercise-induced cardiac hypertrophy[119]. Conversely, forced over-expression of Akt in the heart protects cardiomyocytes from hypoxic injury and apoptosis[120, 121], supporting the notion that Akt could contribute to exercise-induced cardioprotection. Taken together, these studies collectively establish the IGF-1/PI3K/Akt signaling pathway as a central mediator of the cardiac exercise response.

Genome-wide transcriptome analyses comparing exercised hearts to hearts subjected to TAC, also demonstrated distinct sets of transcriptional regulators regulated in physiological and pathological hypertrophy[122]. Moreover, this screen identified a transcriptional pathway downstream of C/EBPβ, a member of the bHLH family of DNA-binding transcription factors, as downregulated with exercise. Reduction of C/EBPβ *in vitro* and *in vivo* was sufficient to recapitulate many of exercise-related phenotypes including a similar gene expression profile, cardiomyocyte hypertrophy, and protection against HF. Notably this pathway is connected to the cardioprotective effects of Akt signaling. Forced over-expression of C/EBPβ in cardiomyocytes blocks Akt1-induced expression of genes characteristic of physiologic hypertrophy, and conversely, Akt1 over-expression downregulates C/EBPβ expression.

In addition, work from our lab and others have shown that microRNAs (miRNAs) and exercise protocols play important roles in the cardiac growth response to exercise[123]. Exercise protocols vary widely, and the growth responses of the heart to different experimental designs are not identical (Table 2)[124]. In comparing the differential expression of miRNAs in the hearts of mice that were exercised with forced swimming versus voluntary wheel running, hearts of swum mice had 55 differentially expressed miRNAs compared to sedentary controls, while hearts from wheel run mice had 124 such miRNAs[125]. Sixteen miRNAs were concordantly regulated in both exercise models, with miRNA-222 proving to be a particularly potent regulator of cardiomyocyte growth and proliferation *in vitro*.

Subsequent *in vivo* studies showed that miRNA-222 was required for exercise-induced hypertrophy, and its forced expression protected against adverse remodeling after ischemic injury. These results demonstrate that integrating different exercise regimens can be a particularly robust approach to identifying critical biological networks, but also underscore the differential responses elicited by distinct protocols and thus the challenges in comparing the data from one regimen in isolation.

Effects of exercise training on age-related cardiac hypertrophy

The concept of distinct forms of cardiac hypertrophy is particularly relevant in the aging heart. As opposed to young animals, in which aerobic training generally induces some degree of hypertrophy in the heart[124], training studies in senescent animals have shown extensive variability in the cardiac growth response to exercise[126–133] with a substantial number of studies indicating that it can paradoxically reverse aged-related hypertrophy (Table 2).

A small subset of these studies have evaluated the effects of exercise training on cardiomyocyte growth in the aged heart. Kwak and colleagues trained young (3 month) and old (24 month) F344 rats on a high intensity (75% VO2max) running protocol for 12 weeks[130]. While training induced cardiomyocyte hypertrophy in the young rats, it resulted in regression of cardiomyocyte size (69% decrease in cross-sectional area) in the aged cohort. Alternatively, low-moderate intensity treadmill running or swimming did not affect cardiomyocyte size in 21-month-old Wistar-Kyoto or spontaneously hypertensive rats, despite reductions in blood pressure in the latter group[131, 132]. Moreover, 10 weeks of low-intensity treadmill running was sufficient to induce cardiomyocyte hypertrophy in aged (24–26 month) C57BL/6 mice [85].

Differences in training protocols and animal models make it inherently difficult to directly compare studies (Table 2). Additionally, only a few studies adequately address the blood pressuring lowering effects of exercise, which are particularly relevant in assessing cardiac growth in the context of aging. However, collectively what these data again seem to indicate is that training intensity and age may be critical determinants in exercise-mediated modulation of cardiac aging phenotypes, specifically with repression of age-related cardiac hypertrophy generally occurring in older animals subjected to higher intensity protocols.

Given the discrepancies among studies, it is not surprising that the molecular basis for the potentially disparate effects of exercise-mediated growth in young versus old hearts is not entirely clear. It is postulated that exercise's cytoprotective effects may improve survival in senescent cardiomyocytes, thus decreasing the stimulus for reactive pathologic hypertrophy. Indeed, hearts from exercise-trained aged rats demonstrate reductions in numerous apoptotic indices that are elevated in the aging myocardium[130, 133, 134]. However, whether these exercise-induced changes translate to less cell death and diminish the trigger for pathologic growth in the aged heart is not proven. Moreover, recent work has shown that pro-apoptotic caspase pathways can directly induce pathologic growth in adult cardiomyocytes[135], suggesting an alternative mechanism by which exercise-induced inhibition of apoptotic pathways may actually directly suppress pathologic growth in the aged heart.

The underlying signaling mechanisms by which exercise potentially improves survival of aged cardiomyocytes may be related to the cardioprotective effects of the IGF1/PI3K/Akt pathway. Cardiac-specific over-expression of IGF1[136], PI3K[137], and Akt1[121] have all been shown to improve cardiomyocyte survival in adult mouse hearts exposed to either TAC or ischemic injury. Importantly, multiple studies have also demonstrated that similar to young animals, aerobic exercise increases Akt phosphorylation in senescent rodent hearts[99, 132, 138], albeit to a lesser extent[132, 134]. Whether lower levels of Akt activity in exercised aged hearts are sufficient to enhance cell survival and suppress pathologic growth pathways, but insufficient to promote physiologic growth may be a plausible explanation.

Ultimately, the variability in cardiac growth responses to exercise between young and old animals likely stems from differences in the substrate of a young versus senescent heart, with apoptotic and pathologic hypertrophy pathways constitutively activated in the latter. Indeed, when young (3 month) and old (18 month) rats are subjected to similar 12-week swimming protocols, while apoptotic markers, MAPK, and calcineurin/NFAT expression decrease in old hearts, they remained unchanged or increased in young hearts, despite increased Akt activity in both groups[134,99]. Interestingly, germline Akt1 knockout mice show an exaggerated growth response to TAC, suggesting that Akt signaling may be capable of directly suppressing pathologic growth pathways in the aged heart[119]. Although the mechanisms by which this occurs in cardiomyocytes are unknown, in other cell types, Akt has been shown to inhibit numerous MAPK pathways (p38, ERK) implicated in pathologic cardiac hypertrophy[139–141].

In addition to Akt signaling, it is important to note that exercise also modulates other growth pathways that may be particularly relevant to the aging heart. Acute treadmill running stimulates neuregulin production in skeletal muscle[142], which has demonstrated anti-apoptotic effects on cardiomyocytes through the ErbB family of tyrosine kinases and potentially downstream PI3K/AKT[143]. Exercise also decreases both skeletal muscle and cardiac myostatin levels in humans and rodents with pathologic hypertrophy[144, 145]. While the precise role of myostatin and its close homologue GDF11 in age-related cardiac hypertrophy awaits clarification, it may be that exercise-induced inhibition of this pathway induces a similar pattern of Akt activity that could potentially inhibit pathologic growth pathways in the aged heart. Indeed, *in vitro* studies have demonstrated that myostatin inhibition drives cardiomyocyte growth through Akt activation[146]. Furthermore, while physiologic versus pathologic growth pathways are largely distinct, there is some overlap. For example, while calcineurin/NFAT signaling is primarily a regulator of pathologic growth of the heart, there is evidence indicating that it also mediates cardioprotective effects and may be necessary in certain physiological growth settings[147, 148]. Ultimately, how exercise dynamically regulates the various signaling pathways involved in age-related cardiomyocyte hypertrophy is still largely unknown and remains a fertile area for future research.

Exercise and mitochondrial dysfunction in the aged heart

The heart requires an enormous amount of energy, primarily derived from fatty acid oxidation and subsequent ATP production within mitochondria. The ability to fulfill this energy requirement, especially under stress, is impaired in the aged heart due to

mitochondrial dysfunction. The mitochondrial theory of aging is a decades-old idea[149], with the underlying premise that oxidative stress increases with age and causes a gradual accumulation of mitochondrial damage and electron transport chain dysfunction[150–153]. Increased levels of free radicals in the aged heart lead to impaired mitochondria, which in turn produce more reactive oxygen species (ROS) resulting in a downward spiral in cardiac performance. Early studies in Drosophila overexpressing ROS scavenging enzymes and in mice with enhanced resistance to oxidative stress demonstrate increased lifespan, as do models of caloric restriction[154–156]. However, more recent studies suggest the relationship between ROS and mitochondrial DNA damage leading to aged phenotypes is not so straightforward, and that widespread ROS elevation in somatic tissues may not be the root cause of aging. In fact, certain levels of ROS may be instrumental for maintaining tissue homeostasis and regenerative potential. In the context of this ongoing debate, we will discuss how the interplay between ROS and mitochondrial function impacts cardiac performance during aging, and the mechanisms by which exercise may play a beneficial role in restoring cardiac energetics.

Mitochondrial dysfunction in aging

Senescence heralds an indisputable decline in mitochondrial function. Mitochondrial DNA (mtDNA) lacks protective histones and is in close proximity to high levels of ROS, and thus is particularly susceptible to oxidation[157]. DNA mutation rate is 10 to 20-fold higher in mitochondria than in nuclei. The role of mtDNA damage in aging is dramatically revealed in Mutator mice. These animals harbor defective proofreading by the mitochondrial DNA polymerase gamma (PolG) and thus carry significant mtDNA deletions and five-fold more point mutations[158, 159]. While this degree of mtDNA damage exceeds that observed in normal aging, no genetic model can represent all the progressive changes that mitochondria undergo. Nevertheless, these mice display global attributes of premature aging, and cardiac senescence in the form of hypertrophy, increased fibrosis, and impaired systolic and diastolic function by eight months of age. Tissues of PolG Mutator mice show decreased levels of mitochondrial biogenesis, diminished respiratory capacity, and increased apoptosis[159, 160]. Interestingly, while Mutator mice do not show increased levels of ROS[159, 161], the expression of a mitochondrial specific catalase partially reverses their cardiac findings[162]. This supports the idea that ROS reduction ameliorates the accumulation of mtDNA mutations and that oxidative stress specifically in mitochondria is a major factor leading to the progerian phenotype.

Given that Mutator mice do not reveal dramatically altered levels of oxygen free radicals or oxidative damage, attention has turned toward possible mechanisms of premature aging that rely less on global increases in ROS, but on subtle alterations in subpopulations of cells. Cellular dysfunction or demise may result when a certain threshold of mutational burden is crossed, or if DNA damage of critical subunits of mitochondrial metabolism results in ineffective respiration, resulting in a heterogeneous response within the myocardium[153, 163]. Mitochondrial decline creating a cellular mosaic in aged human hearts was first exemplified by the arbitrary distribution of cardiomyocytes with undetectable cytochrome *c* oxidase activity[164], and similarly observed in mice lacking mitochondrial transcription factor A (Tfam) in heart and skeletal muscle[165]. The latter develop dilated cardiomyopathy and lethal

conduction blocks. A mosaic of mitochondrial dysfunction in hearts is also observed in mice with a dominant-negative, cardiac-specific mitochondrial helicase, which accelerates the accumulation of mtDNA deletions[166]. Aging mice carrying this mutant gene develop diffuse respiratory deficiency that ultimately manifests as arrhythmias, possibly secondary to aberrant Ca^{2+} handling. A heterogeneous response to mtDNA mutation that ultimately contributes to the progeroid phenotype may also derive from stem cell reservoirs that are particularly vulnerable to ROS elevation. Tissue-specific depots of somatic stem cells are crucial for repair and regeneration[167]. PolG Mutator mice show impaired neural and hematopoietic progenitor cell self-renewal as early as embryogenesis, which can be rescued by administering the antioxidant N-acetylcysteine (NAC) to pregnant females[168].

Benefits of exercise training on mitochondrial preservation

Substantial evidence supports a role for exercise in mitochondrial preservation[169, 170]. Four weeks of voluntary treadmill running in 7–9 week old mice increases the mitochondrial number and volume in their left ventricles[171]. Exercising Mutator mice on a treadmill for five months attenuates their cardiac hypertrophy and fibrosis, in addition to protecting against apoptosis and the decrease in complexes of the mitochondrial respiratory chain in the heart[172]. As with catalase overexpression, the cardioprotective benefits of exercise in PolG mice likely involve ROS detoxifying mechanisms. Indeed, exercise in a variety of tissues, including the heart, has been shown to increase antioxidant capacity by augmenting ROS scavenging enzymes such as catalase, superoxide dismutase, and glutathione peroxidase[173–178].

An integral relationship exists between exercise and transcriptional regulators that limit ROS levels. These factors include the family of PPAR-gamma coactivators, nuclear factor-erythroid-derived 2-like 2 (NFE2L2), and the sirtuin family (SIRTs, silent information regulators). PGC-1α and β, regulators of mitochondrial biogenesis and respiratory capacity, coactivate nuclear respiratory factor 1 and 2 (NRF1 and 2) and estrogen-related receptors in the induction of genes important for oxidative phosphorylation and other mitochondrial processes[179, 180]. Chief among these is Tfam, which controls mitochondrial gene transcription as well as replication. Long-term and short-term endurance exercise increases PGC-1α expression in cardiac and skeletal muscle[181–184]. Exercise, at least in part through β-adrenergic signaling, augments PGC-1α activity and nuclear translocation, resulting in greater mitochondrial biogenesis[183, 185]. In contrast, PGC-1 shows reduced muscle expression in aging, coincident with decreased mitochondrial function[186, 187]. The lower mtDNA content, impaired complex IV activity, and decreased ejection fraction of PolG hearts are largely corrected by the forced expression of PGC-1α[188]. The cardio-protective effects of PGC-1 likely are due, at least in part, to its ROS-lowering effects, as PGC-1α induces GPx1 and SOD2 in models of neurodegeneration [189]. It is unclear whether the benefit comes solely from increased levels of PGC-1α in the heart, or from a systemic contribution from concurrent PGC-1α overexpression in skeletal muscle. Aged mice carrying this MCK-PGC-1α transgene have improved whole body metabolism in the form of greater insulin sensitivity and reduced sarcopenia and chronic inflammation[190].

Exercise enhances antioxidant defenses and restores redox homeostasis in the aging myocardium via NFE2L2 as well. NFE2L2 *trans*-activates genes of the antioxidant response[191], and is coactivated by PGC-1α during oxidative stress[192, 193]. The loss of redox capacity seen in aging is similarly observed in hearts lacking NFE2L2 [194, 195]. While aging hearts exhibit reduced NFE2L2-dependent antioxidant mechanisms, both acute exercise and several weeks of moderate exercise training in aged mice increase NFE2L2 activity and induction of its target pathways to near normal levels seen in young counterparts[194, 196].

SIRTs are NAD^+-dependent deacetylases that regulate cellular health and longevity. As sensors of nutrient flux and redox states, they help to maintain metabolic homeostasis. Two members in particular, SIRT1 and SIRT3, play important roles both in the aged myocardium and in antioxidant pathways. SIRT1 activates hypertrophic pathways via activation of AKT, and its forced high expression produces cardiac dysfunction[197]. In contrast, more moderate levels of SIRT1 transgenic expression reduce age-related hypertrophy, fibrosis, and dysfunction, as well as damage from oxidative stress from paraquat[198, 199]. Mice lacking SIRT3 have the hallmarks of premature aging, and show greater hypertrophy and fibrosis in response to the pressure overload of transverse aortic banding, while SIRT3 overexpression confers resistance to hypertrophy driven by angiotensin-II[200, 201]. Like SIRT1, SIRT3 protects against oxidative stress, in large part through FOXO3a-dependent mechanisms that induce superoxide dismutase and catalase[202]. Notably, these two sirtuins are upregulated during exercise in heart and/or skeletal muscle, and are positive modulators of PGC-1α activity [134, 203–208]. Caloric restriction, likely in concert with SIRTs, helps preserve energy handling in the aging heart and reduce cardiomyocyte apoptosis[8]. Like exercise, it induces PGC-1α in the heart and leads to preserved mitochondrial function during aging [209].

Even in the setting of a heterogeneous response to mtDNA damage within the myocardium during aging, it is likely that exercise nevertheless mitigates damage to discrete subsets of cells that are more susceptible to the effects of ROS. In skeletal muscle at least, moderate intensity endurance exercise in rats protects against the age-associated loss of satellite cells[210]. Interestingly, despite the large body of evidence supporting a causal relationship between ROS and mitochondrial dysfunction in cardiac senescence, nonspecific reduction of ROS has led to surprising results. In clinical trials, antioxidant dietary supplements are not associated with reduced mortality, but rather, in the case of beta carotene, vitamin A, and vitamin E, increased mortality[211]. Some studies paint a more complex picture, suggesting that an exercise-induced *increase* in ROS signals to and activates endogenous mechanisms of antioxidant defense. In both human and rat skeletal muscle, oral administration of the antioxidant vitamin C reduces mitochondrial biogenesis induced by exercise, and lowers the expression of PGC-1α, NRF1, Tfam, and cytochrome c[212]. The combination of vitamins C and E likewise blunt exercise-mediated increases in PGC-1α, PGC-1β, and ROS scavengers in skeletal muscle in healthy human subjects[213]. These studies highlight the delicate balance between the harmful effects of excessive ROS that accelerates senescence and the requirement for some basal level of ROS that maintains critical signaling pathways and cellular homeostasis. In the aging heart, this concept of “mitohormesis” surely plays a crucial role in conveying exercise’s benefits.

Can exercise reverse cardiac aging in humans?

As highlighted throughout this review, exercise training in aged animal models has raised the exciting possibility that exercise can reverse cardiac aging phenotypes associated with HF. Whether similar effects can be derived from exercise in older humans, however, has yet to be defined.

Cross-sectional studies comparing sedentary and athletic older adults, have suggested that lifelong physical activity is associated with less age-related changes in the heart[63, 214–216]. However, inherent limitations in cross-sectional analyses include potential selection bias of "fitter" individuals and those adhering to healthier lifestyles leading to unrecognized confounding or even "reverse causality" in which individuals with better cardiac function are more likely to be lifelong exercisers. Thus, it is impossible to conclude from such studies whether lifelong exercise is causally related to these changes. Furthermore, whether exercise can actually *reverse* established age-related myocardial changes, and if so, whether these changes are directly causal in improving exercise capacity or cardiovascular outcomes in the elderly, remain unknown.

A number of small prospective studies have attempted to address such questions by looking at the effects of exercise training on cardiac structure and function in previously sedentary older adults, with our without HF. While some studies have suggested that training improves resting cardiac parameters associated with HF in the elderly, including diastolic dysfunction[217], systolic reserve capacity[61], and chronotropic incompetence[19], there are an equal number of studies that have shown that training, while similarly improving exercise capacity, does not significantly alter any of these cardiac aging phenotypes[24, 218–220]. Rather, these latter studies argue that exercise-mediated improvements in functional capacity in older adults are primarily derived from peripheral mechanisms of oxygen extraction in the skeletal muscle.

The reasons for these discrepancies are not entirely clear, but similar to training studies in animals, potentially stems from differences in exercise protocols, techniques for measuring cardiac structure/function, and the varying ages of participants studied. Cardiac senescence, as with other aging processes, is a progressive phenomenon. Thus, the often-used inclusion criteria for older adults as simply greater than 65 years, can yield variable results since a 65 year-old's heart is often quite different from an 85 year-old's. Furthermore, with emerging data from aged animals (Table 2) indicating that a sufficient "dose" of exercise is likely necessary to alter established aging phenotypes in the heart[63, 64], what the requisite or optimal dose needed for older humans remains to be determined. Moreover, whether the intensity of exercise utilized in animal studies can be realistically achieved by frail older adults with cardiovascular disease may not be feasible. Ultimately, well-controlled, dose-response studies are needed to begin to answer some of these questions. However, what the growing body of exercise literature in aged animals provides is unique insights into how exercise can modulate the aging process in the heart, and thus, a framework for potentially identifying novel targets for treating age-related heart diseases.

Conclusion

With the rapidly changing distribution of age now occurring at this stage of human evolution, it is becoming increasingly important that we develop a deeper understanding of how cardiac aging impacts the health of our aging population. As highlighted in this review, exercise testing has already provided valuable insights into how cardiac physiology changes with age, and with further refinements will inevitably be a powerful tool for generating and translating discoveries from preclinical animal models. While it still remains to be defined how much exercise training impacts cardiac aging phenotypes in humans, emerging data from aging rodent models has suggested the exciting possibility that exercise can effectively modulate some of the aging process in the heart, and with that provides the promise of identifying novel targets for developing age-specific, tailored therapies for the older patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

HF	Heart failure
CO	Cardiac output
HR	Heart rate
SV	Stroke volume
VO_{2max}	Maximum oxygen consumption
Ca^{2+}	Calcium
β-AR	β-adrenergic receptor
AC	Adenylyl cyclase
PTX	Pertussin toxin
PKA	Protein kinase A
CaMKII	Ca^{2+}/Calmodulin kinase 2
EC	Excitation-contraction
SERCA2a	Sarcoplasmic reticulum Ca^{2+}–ATPase

PLB	Phospholamban
NCX	Na^+/Ca^{2+} exchanger
RyR	Ryanodine receptor
MAPK	Mitogen activated protein kinase
HDAC	Histone deacetylases
NFAT	Nuclear factor of activated T cells
IGF-1	Insulin like growth factor-1
mTOR	Mammalian target of rapamycin
GDF11	Growth differentiation factor 11
TAC	Transverse aortic constriction
ROS	Reactive oxygen species
mtDNA	Mitochondrial DNA
PolG	Polymerase gamma
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1α
NFE2L2	Nuclear factor-erythroid-derived 2-like 2
SIRT	Silent information regulator
NRF	Nuclear respiratory factor
Tfam	Mitochondrial transcription factor A

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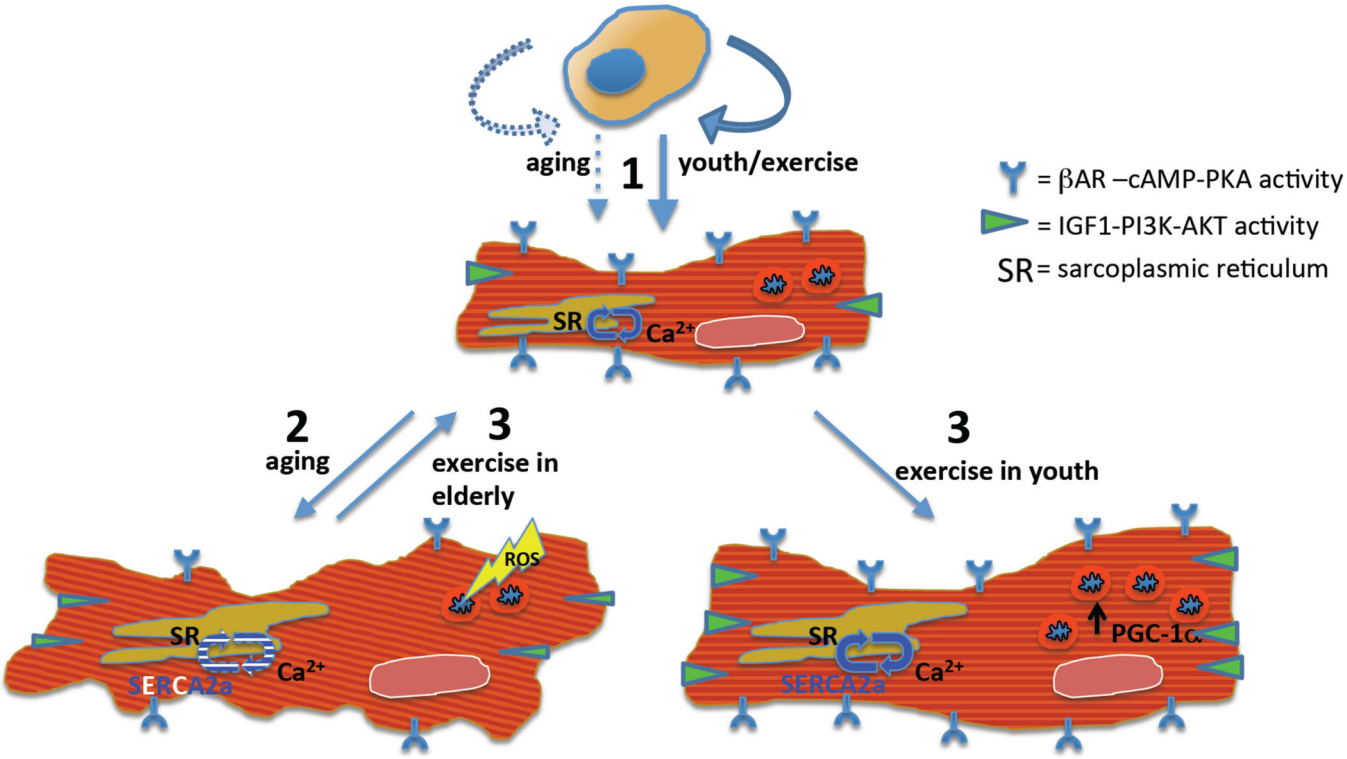

Figure 1.

Multiple mechanisms have been proposed for the impaired cardiomyocyte function observed in aging, and how exercise partially reverses their effects. (1) Diminished cardiac performance in the pathological hypertrophy of aging is linked to decreased IGF1-PI3K-AKT and bAR-cAMP-PKA signaling, decreased SERCA expression and activity and inefficient calcium handling, and mitochondrial dysfunction secondary to excessive ROS. (2) Exercise confers physiological hypertrophy and cardio-protection in the form of enhanced beta-adrenergic and IGF1 signaling, SERCA activity and calcium handling, and mitochondrial dynamics, the latter mediated largely through PGC-1a. (3) These benefits of exercise mitigate the effects of aging (Illustration Credit: Ben Smith).

Table 1

Summary of age-associated changes in cardiovascular performance at peak exercise. Effects of aging are derived from comparison of aerobic exercise testing of healthy young adults (20–30 years) and healthy older adults (60–80 years). CV = cardiovascular. NC = no change. Data summarized from references 19–22.

CV Parameter at Peak Exercise	Effects of Aging
Cardiac output	↓/NC
Heart rate	↓
LV stroke volume	↑/↓/NC
LV end-diastolic volume	↑
LV contractility	↓
Early diastolic filling rate	↓
VO2 max	↓
(A–V) O2 difference	↓

Table 2

Summary of studies in aging rodent models evaluating the effects of aerobic exercise training on cardiac aging phenotypes. Grade is 0% unless specified. Training frequency is 5 days per week unless specified. RSP= Ramped speed protocol. CP= Constant protocol. RDP= Ramped duration protocol. CM = cardiomyocyte. HW = heart weight. LV = left ventricle. BW = body weight. TL = tibial length. BP = blood pressure. Mito = mitochrondrial. (↑) = Increase. (↓) = Decrease. (NC) = No change.

Cardiac Parameter	Aging Animal Model			Exercise Training			Effects of Exercise Training (compared to sedentary control)	Ref
	Species	Strain	Age (mo)	Type	Protocol	Duration (wks)		
Autonomic regulation	Rat	Sprague-Dawley	28	Treadmill running, RSP	30min/day, 20m/min	12	β-AR density (NC), M-R density (NC), Gi activity (↓), AC activity (↑)	Bohm *et al.*, 1993 (47)
	Rat	Wistar-Kyoto	24	Treadmill running, CP	45min/day, 17m/min, 15% (70–85% VO_{2max})	12	β-AR density (↑), AC activity (↑)	Leosco *et al.*, 2007 (62)
	Rat	F344	23	Treadmill running, RDP	75% VO_{2max}	9	Gs activity (NC), AC activity (↑)	Scarpace *et al.*, 1994 (66)
Ca^{2+} handling	Rat	F344	23–24	Treadmill running, RDP	60 min/day, 16 m/min, 5%	8–10	SERCA2a (↑), contractility (↑)	Tate *et al.*, 1996 (80) Tate *et al.*, 1990(81)
	Rat	F344/ BNF1	24	Treadmill running, CP	45min/day 17m/min, 15% (70–85% VO_{2max})	12	Early diastolic filling (↑)	Brenner *et al.*, 2001 (82)
	Rat	F344BN	29	Treadmill running, RSP	60min/day, 5 → 10m/min, 10%	20–28	SERCA2a (NC), RyR (NC), Ca^{2+} cycling (NC)	Thomas *et al.*, 2011 (84)
	Rat	Wistar	21	Swimming CP	90min/day, 35–37°C	8	SERCA2a (↑), contractility (↑)	Iemitsu *et al.*, 2004 (83)
	Mouse	C57BL/6	24	Treadmill running, CP	15min/day, 15m/min	10 (3d/wk)	SERCA2a (NC), NCX (NC)	Walton *et al.*, 2015 (85)
	Mouse	C57BL/6	12	Treadmill running, CP	15min/day, 15m/min	52 (3d/wk)	SERCA2a (↓), NCX (↓)	Walton *et al.*, 2015 (85)
Hypertrophy	Rat	F344/ BNF1	24	Treadmill running, CP	45min/day, 17m/min, 15% (70- 85% VO_{2max})	12	HW/TL (NC)	Brenner *et al.*, 2001 (82)

Cardiac Parameter	Aging Animal Model			Exercise Training			Effects of Exercise Training (compared to sedentary control)	Ref
	Species	Strain	Age (mo)	Type	Protocol	Duration (wks)		
	Rat	F344	25	Treadmill running, RSP, RDP	20 → 60min/day, 4 →15m/min (70–75% VO_{2max})	12	LV (NC), BW (↓), LV/BW (NC), BP (NC)	Choi *et al.*, 2009 (127)
	Rat	F344/ BNF1	29	Treadmill running, RSP	60min/day (in 6×10min reps) 5 →10m/min, 10%	20–28	HW (↓), BW (↓), HW/BW (↑)	Wright *et al.*, 2014 (126)
	Rat	F344BN	29	Treadmill running, RSP	60min/day, 5 → 10m/min, 10%	20–28	HW/BW (↓)	Thomas *et al.*, 2011 (84)
	Rat	F344	24	Treadmill running, CP	60min/day, 15m/min, 15% (70–75% VO_{2max})	12	CM size (↓), apoptosis (↓)	Kwak *et al.*, 2006 (130)
	Rat	Wistar-Kyoto	21	Treadmill running, CP	60min/day (50–60% VO_{2max})	13	CM size (NC), LV/TL (NC), BP (NC)	Rossoni *et al.*, 2011 (131)
	Rat	Wistar	18	Treadmill running, CP	60 min/day, 30m/min	6	HW(↑), BW (↓), HW/BW (↑),	Wang *et al.*, 2014 (128)
	Rat	Sprague-Dawley	28	Treadmill running, RSP	30min/day, 20m/min	12	HW/BW (NC)	Bohm *et al.*, 1993 (47)
	Rat	Wistar	21	Swimming CP	90min/day, 35–37°C	8	LV (−), BW (↓), LV/BW (↑)	Iemitsu *et al.*, 2004 (83)
	Rat	Sprague-Dawley	18	Swimming RDP	20→60min/day, 25±2°C	12	LV (↓), LV/TL (↓)	Liao *et al.*, 2015 (99)
	Rat	Sprague-Dawley	18	Swimming RDP	20→60min/day, 25±2°C	12	LV (↓), LV/TL (↓), apoptosis (↓)	Lai *et al.*, 2014 (134)
	Rat	Wistar	21	Swimming CP	90min/day, 35–37°C	8	CM size (NC), LV (NC), BP (NC)	Iemitsu *et al.*, 2006 (132)
	Mouse	C57BL/6	24	Treadmill running, CP	15min/day, 15m/min	10 (3d/wk)	CM size (↑), HW/BW (↑), HW/TL(↑)	Walton *et al.*, 2015 (85)
	Mouse	C57BL/6	12	Treadmill running, CP	15min/day, 15m/min	52 (3d/wk)	CM size (↑), HW/BW (↑), HW/TL(↑)	Walton *et al.*, 2015 (85)
	Mouse	PolG mutator	3	Treadmill running, CP	45min/day, 15m/min	20 (3d/wk)	HW (↓), Wall thickness (↓)	Safdar *et al.*, 2011 (172)

Cardiac Parameter	Aging Animal Model			Exercise Training			Effects of Exercise Training (compared to sedentary control)	Ref
	Species	Strain	Age (mo)	Type	Protocol	Duration (wks)		
	Mouse	C57BL/6	6–18	Swimming CP	90min session x2/day, 30–32°C	4	LV (↑), LV/BW (↑)	Derumeaux *et al.*, 2008 (129)
Fibrosis	Rat	F344/BN F1	29	Treadmill running, RSP	60min/day (in 6×10min reps), 5 →10m/min, 10%	20–28	Fibrosis (↓), Collagen cross linking (↓)	Wright *et al.*, 2014 (126)
	Rat	F344	25	Treadmill running, RSP, RDP	20 → 60min/day, 4 →15m/min (70–75% VO_{2max})	12	Fibrosis (NC), collagen cross-linking (↓), passive stiffness (↓)	Choi *et al.*, 2009 (127)
	Rat	Sprague-Dawley	18	Swimming RDP	20 →60min/day, 25±2°C,	12	Fibrosis (↓)	Liao *et al.*, 2015 (99)
	Mouse	C57BL/6	24	Treadmill running, CP	15min/day, 15m/min	10 (3d/wk)	Fibrosis (NC)	Walton *et al.*, 2015 (85)
	Mouse	C57BL/6	12	Treadmill running, CP	15min/day, 15m/min	52 (3d/wk)	Fibrosis (↓)	Walton *et al.*, 2015 (85)
	Mouse	C57BL/6	6–18	Swimming CP	90min session x2/day, 30–32°C	4	Fibrosis (↓), contractility (↑), diastolic function (NC)	Derumeaux *et al.*, 2008 (129)
Mitochondrial function	Rat	Wistar	18	Treadmill running, CP	60 min/day, 30m/min,	6	Cardiac mito respiration (↑), ROS (↓)	Wang *et al.*, 2014 (128)
	Rat	Sprague-Dawley	5 wks	Treadmill running, RSP	30min/day, 4.2m/min→ 12m/min at 1m/min/30sec;	36	Cardiac PGC1α (↑), SIRT1 (↑), mito biogenesis (NC),	Bayod *et al.*, 2012 (181)
	Mouse	PolG mutator	3	Treadmill running, CP	45min/day, 15m/min	20 (3d/wk)	Cardiac PGC1α (NC), cardiac mtDNA (↑)	Safdar *et al.*, 2011 (172)

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