Improvements in public health over the past century have led to dramatic increases in life expectancy. By 2030, adults aged >65 years will account for ≈20% of the general population in the United States. Moreover, the oldest demographic groups, consisting of individuals ≥85 years, now represent the fast-growing segment in the United States and are estimated to increase by >230% by 2050. 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 ≈40% of all deaths. Heart failure (HF), in particular, is reaching epidemic proportions with ≈88% of HF deaths and >75% of all HF hospitalizations in the United States now occurring in adults aged ≥65 years.

Although 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 (ie, myocardial infarctions and 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 cellular and molecular levels, which may impair the overall function of the heart as it approaches senescence.

Although 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. Although the aged heart is generally capable of meeting the basal energy requirements of the body, its performance under physiologic 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 reason. Exercise physiology has provided a wealth of knowledge into how age-related changes in cardiac structure and function translate to decreased exercise capacity. With normal aging, VO2max declines by 10% per decade in healthy ambulatory individuals, but this decline notably accelerates at ages >70 years and in HF. 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 2 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 ~40% to 50% of maximal capacity, after which it tends to plateau, and additional augmentation of CO is driven by a further increase in HR.

Although older adults are still capable of augmenting their CO in response to exercise, the relative increase is typically diminished when compared with 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 ~0.7 bpm/y. 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. Importantly, age-related decrease in peak HR strongly correlates with diminished exercise capacity and is an independent predictor of adverse cardiovascular events and mortality.

The impact of aging on SV augmentation with exercise is not as clear with varying degrees of SV reserve reported in different studies. 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. Although 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.

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 (ie, dobutamine). In conjunction with age-associated alterations in peripheral mechanisms of oxygen extraction and utilization in skeletal muscle, inadequate oxygen delivery from impaired cardiac reserve is a major contributor to decreased functional capacity in the elderly, especially those with HF. 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 ~10% per decade in healthy ambulatory individuals, but this decline notably accelerates at ages >70 years and in HF. This suggests 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

Although 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. On the basis of survival data, mice and rats, aged 24 months of age, are typically used to model older humans although even this pre-specified age cutoff must be carefully considered given the wide variation in lifespan across strains. 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.

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. Continuous invasive hemodynamic monitoring in adult (3–4 months) mice has shown that they augment CO by 2-fold (9.6±0.6 mL/min at rest to 18.9±0.9 mL/min at peak exercise) in response to acute exercise. The increased CO is primarily derived from a marked increase in HR (489±18 bpm at rest to 798±9 bpm at peak exercise) and modest SV augmentation. Moreover, similar to humans, as rodents age, exercise capacity progressively declines. VO2max decreases by 28% in healthy 24-month-old C57BL/6J mice when compared with 12-month-old mice. A similar pattern is seen in Fischer 344 x Brown Norway F1 (F344/BNF1) rats, which display 10% and 33% decreases in VO2max at 24 and 35 months, respectively, when compared with 12-month-old rats.

Even in rodents, defining intrinsic factors of aging that influence cardiac reserve and exercise capacity is difficult. Given the central role of the autonomic nervous system on cardiac exercise response, we devote a substantial amount of this review on autonomic dysregulation in the aged heart. Recent studies by Wisloff and colleagues have used a breeding selection strategy in rats based on exercise capacity (referred to as the aerobic hypothesis). From 1996 to 2011, selective breeding of a genetically heterogeneous N:NIH rat stock (28 generations, n=11,606 rats) eventually generated 2 distinct lines that differed in maximal running capacity by 7-fold. Comparative analyses of hearts and isolated cardiomyocytes from aged rats with low and high intrinsic running capacities subsequently identified mitochondrial dysfunction, abnormal calcium (Ca2+) handling, increased hypertrophy, and microvascular dysfunction as key molecular phenotypes in the heart associated with exercise intolerance in aging.

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. Although 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 area.

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.

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% to 15% per decade. In the heart, local norepinephrine levels also increase with age caused by diminished reuptake and increased tissue spill-over. Greater β-AR occupancy by catecholamines triggers a compensatory mechanism in aged cardiomyocytes that results in desensitization of the postsynaptic machinery, and ultimately blunted intracellular Ca2+ transients and impaired inotropic and chronotropic responses to adrenergic stimulation. 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 and rat hearts, implying that at least part of this process is modulated at the receptor level. In addition, 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–mediated Gi ribosylation increase with age. 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

<table>
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<th>Table 1. Summary of Age-Associated Changes in Cardiovascular Performance at Peak Exercise</th>
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<tr>
<td>Cardiac output</td>
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<tr>
<td>Heart rate</td>
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<tr>
<td>LV stroke volume</td>
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<tr>
<td>LV end-diastolic volume</td>
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<tr>
<td>LV contractility</td>
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<tr>
<td>Early diastolic filling rate</td>
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<tr>
<td>VO2max</td>
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<td>(AV) O2 difference</td>
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</table>

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 indicates cardiovascular; LV, left ventricle; and NC, no change. Data summarized.
stimulation cannot be rescued by inhibiting Gi with pertussin tox.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.

Although 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 Ca2+ transients and enhancing cardiac contractility during exercise.49,50 Impaired cAMP/PKA signaling may, in part, be because of persistent activation of Ca2+/calmodulin kinase II (CaMKII), another downstream effector of β-AR signaling. Interestingly, although constitutive β-AR stimulation leads to downregulation of PKA signaling, CaMKII activity remains high. Persistent CaMKII activity can desensitize cardiomyocytes to PKA signaling51,52 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 have 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 seems 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, downregulation 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 mediated through direct modulation of β-AR signaling.

Figure. Multiple mechanisms have been proposed for 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 insulin-like growth factor-I (IGF-I)–phosphatidylinositol 3-kinase (PI3K)–AKT and β-adrenergic receptor (β-AR)–cAMP–protein kinase A (PKA) signaling, decreased sarcoplasmic reticulum Ca2+–ATPase2a (SERCA2a) expression and activity and inefficient calcium handling, and mitochondrial dysfunction secondary to excessive reactive oxygen species (ROS). (2) Exercise confers physiological hypertrophy and cardioprotection in the form of enhanced β-adrenergic and IGF-1 signaling, SERCA2a activity and calcium handling, and mitochondrial dynamics, the latter mediated largely through peroxisome proliferator-activated receptor γ coactivator (PGC)-1α. (3) These benefits of exercise potentially mitigate the effects of aging (Illustration Credit: Ben Smith).
Similar findings have been demonstrated in aged rats. Although 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. A follow-up study, in which 24-month-old Wistar–Kyoto rats were run at 70% to 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.

Although numerous differences in experimental conditions are present between these 2 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 have suggested that a threshold dose of exercise may be necessary to generate significant changes in the heart. In adult rats, direct comparison of moderate (65%–70% VO₂max) and high-intensity treadmill running (85%–90% VO₂max) demonstrated that higher intensity training not only improved exercise capacity to a greater extent but also correlated with a dose-dependent increase in cardiomyocyte hypertrophy, contractility/relaxation, and Ca²⁺ handling. Furthermore, age also seems to play a role in 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. In fact, direct comparison of high-intensity treadmill running (75% VO₂max) in young (3 months) versus old (23 months) F344 rats showed that adrenergically-stimulated AC activity was actually decreased in young rats, while upregulated in older rats.

**Exercise and Ca²⁺ 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 coupling. Numerous age-related changes in key components of cardiomyocyte Ca²⁺ handling, however, impair both the systolic and the diastolic properties of the aged heart.

**Age-Associated Impairments in Ca²⁺ Handling**

To augment myocardial contractility, relaxation, and overall cardiac performance during acute exercise, excitation–contraction coupling must be quickly modified within individual cardiomyocytes to increase the rate of rise and decay of intracellular Ca²⁺ transients. In young cardiomyocytes, peak contractions and Ca²⁺ transients increase and decay more rapidly at higher stimulation frequencies. Although aged cardiomyocytes display similar peak contractions at slow stimulation rates, they produce much smaller increases in peak Ca²⁺ transients and cell shortening at more rapid pacing rates. In addition, rates of Ca²⁺ decay are significantly prolonged in aged cardiomyocytes when 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.

Deficits in intracellular Ca²⁺ handling in aged cardiomyocytes are largely derived from age-associated changes in the proteins involved in excitation–contraction coupling. Decreased levels of sarcoplasmic reticulum Ca²⁺-ATPase2a (SERCA2a) are thought to be a primary mechanism for the prolonged Ca²⁺ transients in the aged myocardium. Cardiac SERCA2a gene transfer in senescent rats restores diastolic function back to youthful levels. In addition, aged-associated alterations in SERCA2a regulatory proteins, including phospholamban, PKA, and CaMKII, have also been documented in the aged heart, with the direction of these changes expected to decrease SERCA2a activity and prolong Ca²⁺ transients. Evidence of age-related changes in other proteins involved in cardiomyocyte Ca²⁺ regulation, including the Na⁺/Ca²⁺ exchanger, ryanodine receptors, and calsequestrin, has not been as consistent or would not necessarily be expected to significantly alter Ca²⁺ transients.

**Effects of Exercise Training on Ca²⁺ Handling in the Aged Heart**

Whether exercise training can improve intracellular Ca²⁺ 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 Ca²⁺ transients in cardiomyocytes and subsequent improvements in systolic and diastolic functions. The mechanisms for these exercise-induced alterations in Ca²⁺ cycling in young hearts are potentially mediated through more effective coupling of L-type Ca²⁺ channels and ryanodine receptors, increased SERCA2a and Na⁺/Ca²⁺ exchanger expression, enhanced SERCA2a function via transient CaMKII activation or phospholamban inhibition, and improved myofilament Ca²⁺ sensitivity.

Aerobic training studies in aged rodents suggest that these benefits are not limited to young animals and seem to be primarily driven by enhanced SERCA2a expression. Eight to 10 weeks of treadmill running increase SERCA2a levels in the hearts of 24-month-old F344 rats. Furthermore, isolated cardiomyocytes from these rats display improved Ca²⁺ cycling and more rapid contractility and relaxation times. Twelve weeks of high-intensity treadmill running (70%–85% VO₂max) in young (6 months) and old (24 months) F344/NDF1 rats also largely reverse 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, potentially through improved Ca²⁺ cycling. Swimming old (21 months) Wistar rats also induces similar increases in cardiac SERCA2a expression. However, other studies have demonstrated that SERCA2a and other related Ca²⁺ channels (ie, ryanodine receptor, Na⁺/Ca²⁺ exchanger) are not increased in aged rodents by aerobic training. 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 and is associated with diastolic dysfunction, HF, and mortality in the elderly. Although age-related vascular remodeling undoubtedly influences cardiomyocyte growth in the aged heart, both human and animal...
Table 2. Summary of Studies in Aging Rodent Models Evaluating the Effects of Aerobic Exercise Training on Cardiac Aging Phenotypes

<table>
<thead>
<tr>
<th>Cardiac Parameter</th>
<th>Aging Animal Model</th>
<th>Exercise Training</th>
<th>Effects of Exercise Training (Compared With Sedentary Control)</th>
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<tbody>
<tr>
<td>Autonomic regulation</td>
<td>Rat Sprague–Dawley</td>
<td>Treadmill running, RSP</td>
<td>β-AR density (NC), M-R density (NC), Gi (↑), AC activity (↑)</td>
<td>Böhm et al52</td>
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<tr>
<td></td>
<td>Rat Wistar–Kyoto</td>
<td>Treadmill running, CP</td>
<td>β-AR density (↑), Ca2+ activity (↑)</td>
<td>Lesco et al42</td>
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<td></td>
<td>F344</td>
<td>Treadmill running, RDP</td>
<td>GS activity (NC), AC activity (↑)</td>
<td>Scarpale et al84</td>
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<td></td>
<td>F344</td>
<td>Treadmill running, RDP</td>
<td>SERCA2a (↑), contractility (↑)</td>
<td>Tate et al41,81</td>
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<tr>
<td></td>
<td>F344/BNF1</td>
<td>Treadmill running, RSP</td>
<td>Early diastolic filling (↑)</td>
<td>Brenner et al22</td>
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<td></td>
<td>Rat F344BN</td>
<td>Treadmill running, RSP</td>
<td>SERCA2a (NC), RyR (NC), Ca2+ cycling (NC)</td>
<td>Thomas et al84</td>
</tr>
<tr>
<td></td>
<td>Rat Wistar</td>
<td>Swimming, CP</td>
<td>LW (↑), LW/BW (↑), LV (↑), HW/BW (↑)</td>
<td>Wright et al24</td>
</tr>
<tr>
<td></td>
<td>Mouse C57BL/6</td>
<td>Treadmill running, CP</td>
<td>HW (↑)</td>
<td>Thomas et al84</td>
</tr>
<tr>
<td></td>
<td>Mouse C57BL/6</td>
<td>Treadmill running, CP</td>
<td>CM size (↑), apoptosis (↑)</td>
<td>Kawk et al94</td>
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<tr>
<td></td>
<td>F344/BNF1</td>
<td>Treadmill running, RSP</td>
<td>CM size (NC), LV/T (NC), BP (↑)</td>
<td>Rossini et al171</td>
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<tr>
<td></td>
<td>Rat Wistar</td>
<td>Treadmill running, CP</td>
<td>LV (↑), BW (↑), LV/BW (↑)</td>
<td>Wang et al176</td>
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<tr>
<td></td>
<td>Rat Sprague–Dawley</td>
<td>Treadmill running, RSP</td>
<td>HW(↑), BW (↑), HW/BW (↑)</td>
<td>Böhm et al47</td>
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<tr>
<td></td>
<td>Rat Wistar</td>
<td>Swimming, CP</td>
<td>LV (↑), HW/T (↑)</td>
<td>Iemitsu et al52</td>
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<tr>
<td></td>
<td>Rat Sprague–Dawley</td>
<td>Swimming, RDP</td>
<td>HW (↑), HW/BW (↑)</td>
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<td></td>
<td>Rat Sprague–Dawley</td>
<td>Swimming, RDP</td>
<td>LV (↑), LV/T, LV/BW (↓)</td>
<td>Lai et al24</td>
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<td></td>
<td>Rat Wistar</td>
<td>Swimming, CP</td>
<td>CM size (↑), HW/BW (↑), HW/T (↑)</td>
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<tr>
<td></td>
<td>Mouse C57BL/6</td>
<td>Treadmill running, CP</td>
<td>CM size (↑), HW/BW (↑), HW/T (↑)</td>
<td>Walton et al48</td>
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<td></td>
<td>Mouse PolG mutator</td>
<td>Treadmill running, CP</td>
<td>CM size (↑), LV/T (↑), BP (↑)</td>
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<td></td>
<td>Mouse C57BL/6</td>
<td>Swimming, CP</td>
<td>HW (↑), Wall thickness (↑)</td>
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<td></td>
<td></td>
<td></td>
<td>LV (↑), LV/BW (↑)</td>
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<tr>
<td>Fibrosis</td>
<td>Rat F344/BNF1</td>
<td>Treadmill running, RSP</td>
<td>Fibrosis (↑), collagen cross-linking (↑)</td>
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<tr>
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<td>Rat F344</td>
<td>Treadmill running, RSP</td>
<td>Fibrosis (NC), collagen cross-linking (↑), passive stiffness (↑)</td>
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<tr>
<td></td>
<td>Rat Sprague–Dawley</td>
<td>Swimming, RDP</td>
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<td>Mouse C57BL/6</td>
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<tr>
<td></td>
<td>Mouse C57BL/6</td>
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<tr>
<td></td>
<td>Mouse C57BL/6</td>
<td>Swimming, CP</td>
<td>Fibrosis (↑), contractility (↑), diastolic function (NC)</td>
<td>Derumeaux et al129</td>
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(Continued)
studies indicate that mechanisms independent of changing hemodynamics also contribute. Cardiomyocyte hypertrophy in the aged heart may, in part, be a compensatory response to a cumulative loss of myocytes with normal aging. Declining regenerative potential in the aged heart seems insufficient to counterbalance this loss. Although 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.

### Mechanisms of Age-Related Cardiac Hypertrophy

Many of the molecular mechanisms underlying cardiomyocyte hypertrophy in the aged heart seem similar to the intracellular signaling pathways that drive pathologic growth in hypertension and HF. 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 mitogenic-activated protein kinases, histone deacetylases, calcineurin/nuclear factor of activated T cells, and insulin-like growth factor-I (IGF-I)–phosphatidylinositol 3-kinase (PI3K)–AKT–mammalian target of rapamycin pathways. For a detailed discussion of these pathways, see Heineke and Molkentin. Recent work by Egerman et al has highlighted the importance of growth differentiation factor-11 (GDF11), a secreted member of the transforming growth factor-β superfamily, in the regulation of aging and cardiac hypertrophy and longevity.

#### Table 2. Continued

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<th>Effects of Exercise Training (Compared With Sedentary Control)</th>
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<td>Mitochondrial function</td>
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<td>Rat Wistar 18</td>
<td>Treadmill running, CP</td>
<td>60 min/d, 30 m/min, 6</td>
<td>Cardiac mito respiration (↑), ROS (↓)</td>
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<td>Rat Sprague–Dawley 5 wk</td>
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<td>30 min/d, 4.2 m/min→12 m/min at 1 m/min/30 s 36</td>
<td>Cardiac PGC1α (↑), SIRT1 (↑), mito biogenesis (NC), Bayod et al[103]</td>
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<tr>
<td>Mouse PolG mutator 3</td>
<td>Treadmill running, CP</td>
<td>45 min/d, 15 m/min 20 (3 d/wk)</td>
<td>Cardiac mtDNA, mito respiration (↑), cardiac mtDNA (↑)</td>
<td>Safdar et al[112]</td>
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</tbody>
</table>

Grade is 0% unless specified. Training frequency is 5 days/wk unless specified. (↑) indicates increase; (↓) decrease; β-AR, β-adrenergic receptor; AC, adenyl cyclase; BP, blood pressure; BW, body weight; CM, cardiomyocyte; CP, constant protocol; HW, heart weight; LV, left ventricular weight; M-R, muscarinic receptor; NC, No change; NCX, Na\(^+\)/Ca\(^{2+}\) exchanger; mito, mitochondrial; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; RDP, ramped duration protocol; ROS, reactive oxygen species; RSP, ramped speed protocol; RyR, ryanodine receptor; SERCA2a, sarcoplasmic reticulum Ca\(^{2+}\)-ATPase; SIRT1, silent information regulator; TL, tibial length; and VO2max, maximum oxygen consumption.

growth in aging hearts. Similarly, cardiogenic suppression of PI3K, as well as systemic mammalian target of rapamycin inhibition with rapamycin, reverses hypertrophy and lipofuscin accumulation in aged murine hearts. The role of histone deacetylases, particularly NAD-dependent sirtuins, has 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 et al found that systemic levels of growth differentiation factor-11 (GDF11), a secreted member of the transforming growth factor-β superfamily, decline with normal aging. 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 et al, however, found that GDF11 therapy did not alter cardiomyocyte hypertrophy in old C57BL/6 mice and, moreover, did not affect cardiac function. 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 transforming growth factor-β superfamily member (also known as GDF8). Aging studies in germline myostatin knockout mice have suggested that although systemic myostatin inhibition induces modest cardiac hypertrophy in senescent mice, it also decreases myocardial fibrosis and improves systolic function. Indeed, both hearts and isolated cardiomyocytes from aged germline knockouts demonstrate improved β-adrenergic responsiveness, Ca\(^{2+}\) handling, and enhanced contractility to sympathetic stimulation. 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 cardiogenic-specific myostatin knockout mice, and likewise, GDF11 therapy has no effect on TAC-induced pathologic hypertrophy. Recent work by Egerman et al has highlighted the
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. 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 2 kinds of cardiac growth different, but the underlying molecular mechanisms are also quite distinct.

Exercise-induced hypertrophy is mediated largely through increased IGF-1 signaling in the heart. 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. 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 110β isoform also inhibits exercise-induced cardiac growth. Similarly, germline deletion of the PI3K-effector, Akt1, abolishes exercise-induced cardiac hypertrophy. Conversely, forced overexpression of Akt in the heart protects cardiomyocytes from hypoxic injury and apoptosis, 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. Moreover, this screen identified a transcriptional pathway downstream of CCAAT/enhancer-binding protein beta (C/EBPβ), a member of the basic helix-loop-helix 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 intersects with Akt signaling. Forced overexpression of C/EBPβ in cardiomyocytes blocks Akt1-induced expression of genes characteristic of physiologic hypertrophy, and conversely, Akt1 overexpression downregulates C/EBPβ expression.

In addition, work from our laboratory and others have shown that micro-RNAs (miRNAs) and exercise protocols play important roles in the cardiac growth response to exercise. Exercise protocols vary widely, and the growth responses of the heart to different experimental designs are not identical. 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 when compared with sedentary controls, whereas hearts from wheel run mice had 124 such miRNAs. 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 not only 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 1 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 the case in young animals, in which aerobic training generally induces some degree of hypertrophy, training studies in senescent animals have shown extensive variability in the cardiac growth response to exercise, with a substantial number of studies indicating that it can paradoxically reverse aged-related hypertrophy.

A small subset of these studies has evaluated the effects of exercise training on cardiomyocyte growth in the aged heart. Kwak et al trained young (3 months) and old (24 months) F344 rats on a high-intensity running protocol (75% VO2max) for 12 weeks. Although 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. Moreover, 10 weeks of low-intensity treadmill running were sufficient to induce cardiomyocyte hypertrophy in aged (24–26 months) C57BL/6 mice.

Differences in training protocols and animal models make it inherently difficult to directly compare studies. In addition, only a few studies adequately address the blood pressure–lowering effects of exercise, which are particularly relevant in assessing cardiac growth in the context of aging. However, collectively these data again seem to indicate that training intensity and age are 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. 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 proapoptotic caspase pathways can directly induce pathologic growth in adult
cardiomyocytes, suggesting an alternative mechanism by which exercise-induced inhibition of apoptotic pathways may 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 IGF-1/P38K/Akt pathway. Cardiac-specific overexpression of IGF-144, PI3K, and Akt145,46 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 aerobic exercise increases Akt phosphorylation in senescent rodent hearts132,138 to a similar albeit a lesser extent.132,134 It is plausible that partially restored 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.

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 months) and old (18 months) rats are subjected to similar 12-week swimming protocols, apoptotic markers, mitogen-activated protein kinase, and calcineurin/nuclear factor of activated T-cell expression decrease in old hearts, but remain unchanged or increased in young hearts, despite increased Akt activity in both groups.99,134 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 mitogen-activated protein kinase pathways (p38 and extracellular signal-regulated kinase) 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 antiapoptotic effects on cardiomyocytes through the ErbB family of tyrosine kinases and calcineurin/nuclear factor of activated T-cell expression decrease in old hearts, but remain unchanged or increased in young hearts, despite increased Akt activity in both groups.99,134 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 mitogen-activated protein kinase pathways (p38 and extracellular signal-regulated kinase) implicated in pathologic cardiac hypertrophy.139–141

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 largely due to defective mitochondria. The mitochondrial theory of aging is a decades-old idea149 with the underlying premise that oxidative stress increases with age and causes a gradual accumulation of mitochondrial damage and electron transport chain dysfunction.150–152 Increased levels of free radicals in the aged heart lead to impaired mitochondrial function, 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, to do models of caloric restriction.154–156 However, more recent studies suggest that the relationship between ROS and mitochondrial DNA (mtDNA) 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. mtDNA lacks protective histones and is in close proximity to high levels of ROS, and thus is particularly susceptible to oxidation.153 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 mtDNA polymerase gamma (PolG) and thus carry significant mtDNA deletions and 5-fold more point mutations.158,159 Although 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 functions by 8 months of age. Tissues of PolG Mutator mice show decreased levels of mitochondrial biogenesis, diminished respiratory capacity, and increased apoptosis.159,160 Interestingly, although Mutator mice do not show increased levels of ROS,160,161 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 in heart and skeletal muscles.165 The latter develop dilated cardiomyopathy and lethal conduction block. 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 Ca2+ 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 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- to 9-week-old mice increase the mitochondrial number and volume in their left ventricles.171 Exercising Mutator mice on a treadmill for 5 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 peroxisome proliferator-activated receptor γ coactivators, nuclear factor-erythroid-derived 2-like 2 (NFE2L2), and the sirtuin family (silent information regulators [SIRTs]). Peroxisome proliferator-activated receptor γ coactivator (PGC)-1α and β, regulators of mitochondrial biogenesis and respiratory capacity, coactivate nuclear respiratory factor 1 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 mitochondrial transcription factor A, which controls mitochondrial gene transcription and replication. Long- and short-term endurance exercise increases PGC-1α expression in cardiac and skeletal muscles.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 cardioprotective effects of PGC-1 are likely mediated in part through its ROS-lowering effects, as PGC-1α induces GPx1 and superoxide dismutase 2 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 muscle creatine kinase (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 response191 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 Although 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 in both aged myocardium and 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, whereas SIRT3 overexpression confers resistance to hypertrophy driven by angiotensin II.200,201 Like SIRT1, SIRT3 protects against oxidative stress, in large part through FOXO3α-dependent mechanisms that induce superoxide dismutase and catalase.202 Notably, these 2 sirtuins are upregulated during exercise in heart and skeletal muscles and are positive modulators of PGC-1α activity.204-208 Caloric restriction, likely in concert with SIRTs, helps preserve energy handling in the aging heart and reduces cardiomyocyte apoptosis.5 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 aged myocardium, 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.20

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 β carotene, vitamin A, and vitamin E, increased mortality.21 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 muscles, oral administration of the antioxidant vitamin C reduces mitochondrial biogenesis induced by exercise and lowers the expression of PGC-1α, nuclear respiratory factor 1, mitochondrial transcription factor A, and cytochrome c.212 The combination of vitamins C and E likewise blunts exercise-mediated increases in PGC-1α, PGC-1β, and ROS scavengers in skeletal muscle in healthy human subjects.213 These studies underscore 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 the source of 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.

Many 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 or without HF. Although some studies have suggested that training improves resting cardiac parameters associated with HF in the elderly, including diastolic dysfunction,217 systolic reserve capacity,62 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 as in the case of animal studies potentially stem from differences in exercise protocols, techniques for measuring cardiac structure/function, and the varying ages of participants. Cardiac senescence, as with other aging processes, is a progressive phenomenon. Thus, the often-used inclusion criteria for older adults as simply >65 years can yield variable results because a 65-year-old heart is often 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,213 the requisite or optimal dose needed for older humans remains to be determined. Moreover, the intensity of exercise used in animal studies may not be realistically achieved by frail older adults with cardiovascular disease. Ultimately, well-controlled, dose–response studies are needed to answer these questions. However, the growing body of exercise literature in aged animals provides 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.

Conclusions

The rapidly changing distribution of age in our population demands a deeper understanding of cardiac senescence. 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. Although the impact of exercise training on human cardiac aging phenotypes remains incompletely defined, emerging data from rodent models have suggested the exciting possibility that exercise can effectively modulate the aging process in the heart. These studies hold great promise for identifying novel targets for age-specific, tailored therapies in the older patient.

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Disclosures

None.

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