ARTICLE

Mechanisms of Exercise-Induced Cardiac Remodeling Differ Between Young and Aged Hearts

Emily E. Schmitt[1,2], *Benjamin D. McNair*[1], *Sydney M. Polson*[1], *Ross F. Cook*[1], *and Danielle R. Bruns*[1,2]

[1]Division of Kinesiology & Health, University of Wyoming, Laramie, WY; and [2]Wyoming WWAMI Medical Education, Laramie, WY

SCHMITT, E.E., B.D. MCNAIR, S.M. POLSON, R.F. COOK, and D.R. BRUNS. Mechanisms of exercise-induced cardiac remodeling differ between young and aged hearts. *Exerc. Sport Sci. Rev.*, Vol. 50, No. 3, pp. 137–144, 2022. *Aging induces physiological and molecular changes in the heart that increase the risk for heart disease. Several of these changes are targetable by exercise. We hypothesize that the mechanisms by which exercise improves cardiac function in the aged heart differ from those in the young exercised heart.* **Key Words:** aging, exercise, cardiac remodeling, cardioprotective, cardiovascular fitness

Key Points

- Exercise protects against cardiovascular disease and slows cardiac aging, in part through direct cardiac remodeling.
- The mechanisms responsible for cardiac benefits of exercise in the aged heart are unclear but likely differ from those in the young heart.
- The young heart undergoes physiological hypertrophy and improvements in systolic and diastolic function.
- The aged heart does not undergo hypertrophy, and improvements in cardiac function are modest.
- Fibrosis is absent in the young heart but is reversed by exercise in the aged.

INTRODUCTION

Regular exercise is widely recognized to induce beneficial cardiac adaptations and is among the most cardioprotective interventions identified to date. Cross-sectional studies in humans strongly support the notion that lifelong physical activity is associated with fewer or delayed age-related changes in the heart in both males and females (1,2). In addition, exercise protects against cardiovascular disease and is a significant component of cardiac rehabilitation. This well-established protection by exercise occurs through modification of risk factors, activation of biochemical mechanisms to protect the heart against stress, and *exercise-induced cardiac remodeling*. Exercise-induced cardiac remodeling is defined as structural and functional changes to the heart due to changes in cardiac size, mass, geometry, and function (3). Although exercise-induced cardiac remodeling has been well described in the young heart, the mechanisms by which the aged heart undergoes these structural and functional changes are less clear and are likely distinct from those in the young. To date, few investigations have directly compared exercise-induced cardiac remodeling in the young and aged hearts, and much of what is known about exercise-mediated cardioprotection has been extrapolated from findings reported uniquely in young or aged animals, rather than a rigorous comparison of the two age groups under the same study design. The purpose of this brief review is to identify several mechanisms by which exercise protects the heart and to discuss how these adaptations differ in young and aged hearts. We hypothesize that exercise-induced cardiac remodeling is age specific, resulting in distinct molecular and physiological mechanisms in the aged heart compared with the young. We discuss exercise-induced cardiac remodeling in the setting of chronic adaptations to exercise training, although acute increases in cardiac work also likely differ between young and aged models. Furthermore, although our focus is on cardiac remodeling, we suspect that changes in cardiovascular disease risk factors and activation of cardioprotective pathways also vary in young and aged organisms in response to chronic exercise.

THE AGING HEART

Before discussion of the aging heart and exercise can occur, a definition of age must be reached. Clinically, aging refers to humans 65 yr and older as defined by the Centers for Disease Control and Prevention and World Health Organization. In preclinical models, this roughly extrapolates to 18 months in mice (Jackson Laboratory) and 24 months in rats (4). We note that some contention still exists with regard to these definitions, specifically with respect to chronological versus biological

Address for correspondence: Danielle R. Bruns, Ph.D., University of Wyoming, 1000 E. University Ave, Dept 3196, Laramie, WY 82071 (E-mail: dbruns1@uwyo.edu).
Accepted for publication: December 16, 2021.
Editor: Karyn L. Hamilton, R.D., Ph.D., FACSM

0091-6331/5003/137–144
Exercise and Sport Sciences Reviews
DOI: 10.1249/JES.0000000000000290

age and factors such as frailty and comorbidities. However, for the purposes of this review, our analysis has been restricted to clinical and preclinical reports, which meet these definitions. We also note for the purposes of this review that we have limited our discussion to healthy models, meaning those free from overt cardiovascular disease. However, given the strong correlation between sedentary behavior, aging, and chronic disease, it is likely that the definition of healthy falls on a spectrum of conditions from confirmed healthy to those with undiagnosed occult disease.

The heart undergoes several physiological and molecular changes with aging, many of which are beyond the scope of the current review. Here, we focus on several well-reported changes, which is discussed in the context of exercise. Even in the absence of factors that adversely impact cardiac function (*i.e.*, diabetes, hypertension), the heart remodels with advanced age. Morphologically, the aging heart is characterized by left ventricular (LV) hypertrophy (5) and elevated deposition of extracellular matrix (ECM) proteins (6). Longitudinal observations from the Framingham Heart Study report age-associated increases in LV wall thickness and decreased LV dimensions (7) across the adult life course, along with increases in myocyte cell size (8). Autopsies of human hearts demonstrate higher collagen content in individuals older than 65 yr compared with 20- to 25-yr-olds, even in subjects without overt cardiac disease (6). These changes to cardiac morphology are also noted in aging rodents, with aged mice and rats demonstrating elevated LV chamber size, wall thickness, and hypertrophy alongside higher LV collagen content (9,10). As a result of, or at least in parallel to these morphometric changes, the heart also undergoes changes in cardiac function with advanced age. The aging heart demonstrates diastolic dysfunction with impaired relaxation. Although systolic function is not typically impaired at rest, in response to increased cardiac work such as during exercise, the aged heart displays a diminished ability to improve cardiac inotropic and chronotropic reserve (7,9). Together, these changes result in reduced cardiovascular and cardiorespiratory function and elevated risk for heart disease.

EXERCISE-INDUCED CARDIAC REMODELING IN THE YOUNG AND AGED

Exercise capacity is among the strongest predictors of risk of death in men (11) and women (12). Although exercise capacity is complex and driven by both genetics and environment (13), the overall benefits of exercise to improve cardiac structure and function have been established for decades. Exercise training improves cardiorespiratory fitness in subjects and models of all ages, and undoubtedly lowers cardiovascular risk mortality. Regular exercise induces beneficial structural and functional changes in the heart, collectively referred to as *exercise-induced cardiac remodeling* (3). However, despite clear and robust evidence for exercise as cardiovascular medicine, the mechanisms by which exercise-induced cardiac remodeling occurs in aged versus young hearts are not yet clear. In the following section, we discuss exercise-induced cardiac remodeling and how these mechanisms differ by age. Our discussion describes age-specific adaptation to exercise with a special focus on the contribution of hypertrophy and fibrosis to cardiac function. Although these processes were chosen based on our group's expertise (14,15), as well as available literature in both young and aged models, we would be remiss if we did not mention that other age-specific differences underlie the response to exercise including mitochondrial function and dynamics (16), antioxidant defenses (17), and angiogenesis (18). Furthermore, it is likely that noncardiac adaptations to exercise differ by age such as vascular and skeletal muscle adaptations.

Preclinical Rodent Models of Exercise

Limited access to human cardiac tissue is a major obstacle to understanding the mechanisms of aging and of exercise-induced cardiac remodeling. To circumvent this issue, preclinical models, specifically rodents, have been useful because of similar cardiac aging phenotypes to humans as well as similar exercise physiology (19). The focus of this review is on preclinical rodent models of exercise and cardiac function, although specific human reports are mentioned where warranted. From a preclinical standpoint, most literature utilizes mice and rats that undergo forced treadmill training or voluntary wheel running, with smaller contributions from swim exercise, high-intensity interval training (HIIT), and resistance training. The advantages and disadvantage of preclinical exercise models have been well reviewed elsewhere (20), but in most instances, regardless of the modality, mice and rats undergo predictable cardiac remodeling that recapitulates human adaptations. However, subtle but critical differences exist, especially when considering age. Generally, rodents sprint for short durations in multiple installments over a 24-h period. Therefore, cumulative exercise for a rodent does not directly equate to voluntary physical activity levels in humans who likely do not engage in as many repeated installments. However, given that wheel running is voluntary, it is still generally accepted as mirroring the natural pattern of activity in humans, with some suggestion that it may more accurately represent human voluntary activity with advanced age than other forms of training (20). Although activity is highly strain dependent (4), running wheel distance and speed peak around 12–15 wk of age, then steadily decline because of reductions in both running velocity and duration (21). Therefore, the low engagement of voluntary wheel running can be a barrier to implementation of this modality in aged animals. Forced exercise offers the circumvention of low running distances in aged animals. However, in addition to the psychological and physiological stress of treadmill running, it is often accompanied by disadvantages in circadian timing of exercise with training occurring during the animal's inactive period (20). Furthermore, it can be difficult to age-match for intensity to compare young and aged animals. Awareness of these barriers and selection of appropriate models to answer age-specific questions will enhance the translatability of preclinical findings to the human heart.

Cardiac Function in the Young and Aged

Principal adaptations of cardiovascular function in response to exercise in the young include both improved systolic and diastolic functions. Endurance training increases stroke volume (SV) (22) and cardiac output (CO) to improve delivery of blood to the periphery. Training also induces diastolic remodeling with increased end-diastolic volume (EDV) due to higher LV volumes and improved LV compliance. Together, higher EDV also contributes to higher SV due to Frank-Starling mechanisms (reviewed in (23)).

Exercise-induced changes in cardiac function in the aged heart are more variable and typically diminished in comparison

to the young. Preclinically, a few reports demonstrate modest improvements in ejection fraction (EF) and fractional shortening (24,25) after 8–12 wk of regular endurance training in aged mice and rats. However, in older humans, improvements in systolic function with endurance training are not commonly reported (26). Unpublished data from our group demonstrate that 2 wk of voluntary wheel-running improved systolic function in young mice as measured by higher fractional area change (FAC) and EF. However, these changes were blunted in aged mice (Figs. 1A, B) as evidenced both by the significant interaction between age and running as well as within-age comparisons showing more robust adaptations in the adult heart. We note that in both our unpublished work and the preclinical studies previously mentioned, assessments of systolic function were made at rest, not during exercise. Declines in resting systolic function generally do not occur with aging, but rather declines in systolic reserve characterize the aging heart. Modest evidence exists for improvements of systolic reserve with exercise training in aged rats and humans (reviewed in (19)), although the mechanisms are not yet fully described. Diastolic function, however, does markedly decline with aging. In most preclinical reports, diastolic function improves with exercise training, at least to the extent that it attenuates age-associated impairments in diastolic function (25,27). The mechanism of improved relaxation differs in the young and aged hearts, with improved early diastolic filling in aged but not in adult hearts (27). Distinct mechanisms of exercise-induced diastolic function have also been reported in humans. Six months of progressive aerobic exercise training in men improved peak atrial filling rate in older exercisers while remaining unchanged in young (28). These findings make sense, given that diastolic filling in the aged heart has a larger contribution from atrial filling rather than passive relaxation. However, we do note that exercise-induced changes in diastolic function in humans remain controversial, with many reports suggesting less robust or absent changes in relaxation. Elegant exercise interventions of progressive and vigorous training protocols generally have not demonstrated significant improvements in LV stiffness in men (29) or women (30,31), despite favorable changes in aerobic capacity. Together, although exercise training may improve systolic or diastolic function at rest, these functional changes are modest in comparison to the well-established functional outcomes of training in young hearts.

Hypertrophy in the Young and Aged

Chronic exercise training stimulates LV hypertrophy. This type of hypertrophy, referred to as physiological hypertrophy, is distinct from age-related hypertrophy. Although differences exist with respect to the type of hypertrophy (eccentric or

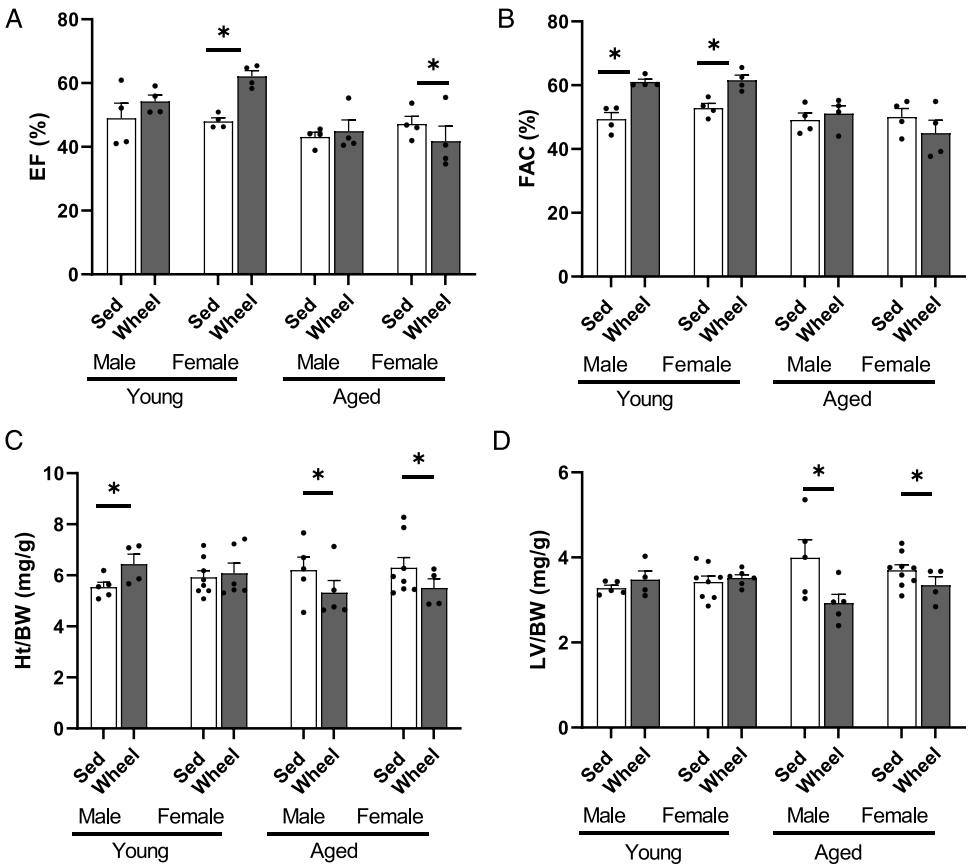

Figure 1. Exercise-induced cardiac remodeling by echocardiography and cardiac morphometrics in young and aged male and female mice. Adult (4- to 6-month-old) or aged (18-month-old) C57Bl6 mice underwent 2 wk of voluntary wheel running. A. Ejection fraction (EF) was higher in adult female mice in response to exercise training but not different in aged mice. B. Fractional area change (FAC) was higher in adult mice while unchanged in aged mice. C. Adult male mice had larger heart weight normalized to body weight (Ht/BW) in response to wheel running, whereas aged mice of both sexes demonstrated a regression of cardiac mass after wheel running. D. Similarly, adult male mice had larger left ventricle weight normalized to body weight (LV/BW) in response to wheel running, whereas aged mice of both sexes had smaller LV/BW. Average nightly running distances were as follows: adult male, 3 ± 0.6 km; adult female, 5 ± 0.7 km; aged male, 1 ± 0.5 km; and aged female, 3 ± 0.9 km. *P < 0.05 sedentary versus wheel within age and sex. Data were analyzed by two-way analysis of variance, followed by Student's t-test within age and sex. Data are expressed as mean ± SEM. Sed, sedentary; Wheel, voluntary wheel running. Bruns DR, unpublished data, 2022.

concentric, due to endurance training or strength training, respectively), exercise-induced hypertrophy is characterized by both higher LV size and volumes. Physiological hypertrophy is accompanied by an increase in LV chamber dimensions, increased LV EDV, and decreased ESV, as well as enhanced left atrial cavity size (32). Targeted genetic investigations in mice have elucidated the pathways responsible for physiological hypertrophy including insulin-like growth factor 1 (IGF1), phosphoinositide 3-kinase (PI3K), and protein kinase Akt (reviewed in (33)). Higher expression of these mediators has been reported in professional athletes (34), further mechanistically linking these molecules to hypertrophic outcomes. Although most of the beneficial reports of exercise on cardiac remodeling have been gleaned from endurance exercise, over the last several years, growing recognition has emerged regarding other forms of exercise, particularly with respect to HIIT and reports of greater changes in LV mass compared with moderate-intensity exercise (35).

In contrast to the wealth of data demonstrating exercise-induced cardiac hypertrophy in young models, extensive variability exists in the aging heart. Although a few studies have reported that moderate-intensity treadmill running increases cardiac mass and myocyte cross-sectional area in 24-month old male mice (36), the bulk of the work to date suggests that hypertrophy is either unchanged (37,38) or paradoxically reversed with exercise training in the aged (16,39). We recently compared the hypertrophic response of young (3-month) and aged (18-month) mice in response to 4 wk of voluntary wheel running (Bruns DR, unpublished data, 2022). We found consistent regression of LV and heart mass in 18-month-old mice — both when expressed as gross morphometric assessment and when normalized to body weight (Figs. 1C, D). This finding that exercise regresses cardiac mass in the aged heart is significant and interesting in light of the observations that antiaging drugs, which improve cardiac function also promote the regression of LV mass (40). Furthermore, the notion that exercise can reverse or attenuate cardiac mass is not without precedence, as young animals engaging in physical activity after or preceding myocardial infarction also demonstrate attenuation of LV hypertrophy (41).

Unlike the molecular mediators for exercise-induced hypertrophy in the young heart, the mechanisms by which the aged heart changes cardiac mass are not well described. Although some work suggests that Akt is activated in response to 8 wk of swim exercise training in rats, whether this is similar in magnitude to the activation elicited by chronic training in young animals is not known because this study did not include a young exercise group (38). IGF1 and PI3K were upregulated in the hearts of middle-aged mice (42) and rats (39) by 12 wk of wheel running or swim training, respectively. However, statistical analyses did not assess whether the magnitude of these changes was the same as in younger animals, nor were older animals included. Exercise likely regulates hypertrophy in the aging heart through myocyte survival. Age-related cardiac hypertrophy is due at least in part to myocyte apoptosis and concomitant reactive hypertrophy to replace lost myocytes. Activation of apoptotic signals in the aged heart is reversed or at least attenuated by exercise training (39,43), suggesting attenuation of cell death may be a mechanism by which exercise attenuates age-associated hypertrophic remodeling. However, it is not yet clear whether reduced apoptotic signals result in attenuated cell death and diminished hypertrophic response. Identification of these mechanisms is important for understanding exercise-mediated changes in cardiac mass and how this response differs in young versus aged hearts.

Clinically, exercise training in older adults also does not seem to be as robustly hypertrophic as in younger subjects. Cross-sectionally, no differences were noted in LV mass between apparently healthy sedentary seniors and master athletes (44). Older women who underwent 12 wk of aerobic, strength, or combined aerobic and strength training saw no change in cardiac mass by echocardiography (31), nor were changes in cardiac structure noted in octogenerians who underwent 9 months of exercise training at 85% of heart rate peak (45). With longer duration and higher-intensity interventions, modest increases in LV mass were noted in previously healthy sedentary seniors (29), perhaps suggesting that higher intensity and volumes of exercise are needed for the hypertrophic response. Although future work is warranted with respect to the intensity, duration, and timing of the exercise intervention and the molecular signals behind exercise-induced remodeling, it does not seem as though the aged heart undergoes similar hypertrophic adaptation as the young.

Fibrosis in the Young and Aged

The aging heart is characterized by excess deposition of ECM proteins, resulting in a fibrotic heart with elevated arrhythmia potential, diastolic deficits, and subtle contractile abnormalities during exercise. Myocardial ECM accumulation is the end result of the balance between synthesis and degradation of ECM proteins. A major component of the ECM is collagen, with collagen content including the summation of all types of collagens that ultimately reflects ECM quality. Excess accumulation of ECM in the aging heart has been suggested to be due to age-associated increases in profibrotic mediators such as transforming growth factor β1 (TGF-β1), as well as declines of mechanisms, which remove the matrix such as metalloproteinases (MMP) (46). Although fibrosis and diastolic function are not always connected, as discussed in greater depth hereinafter, collagen accumulation is undoubtedly significant in the aged heart, given the strong correlation between collagen content and diastolic stiffness (47). Therefore, not surprisingly, exercise emerged as an antifibrotic intervention in the aged heart given its impact on diastolic function (17,48–50). We were unable to find reports of the impact of exercise on fibrosis in the human heart. Given the robust reports of age-associated diastolic dysfunction and ECM deposition in human hearts, it is reasonable to hypothesize that some degree of antifibrotic remodeling occurs in response to exercise; however, the degree to which the ECM reverse remodels is not yet known.

Exercise may promote degradation of collagen and other ECM proteins by MMP, downregulate profibrotic factors, or both. Downregulation of TGF-β1 and other profibrotic molecules was suggested to be responsible for attenuated fibrosis in aged rats that underwent 12 wk of endurance training (51). However, exercise also stimulated the expression of MMP (51). The strongest evidence for mechanisms of reduced ECM deposition with exercise is due to posttranslational modification of collagen proteins — that is, reducing age-related cross-linking. Several studies report unchanged expression of MMP and profibrotic gene expression, but do report attenuation of collagen cross-linking in the aged exercised LV (37,48,49). Additional

support for the hypothesis that the quality of the ECM supports beneficial cardiac remodeling comes from studies demonstrating that exercise training can alter collagen characteristics even if total collagen remains unchanged (37,48). Age-related changes in oxidative stress and inflammation also likely contribute to modifications of ECM proteins via collagen cross-linking. Exercise has well-established antioxidant and anti-inflammatory mechanisms in the young heart, suggesting that similar mechanisms may contribute to a beneficial ECM phenotype in the aged heart as well.

Reports of exercise as an antifibrotic intervention are incredibly sparse in young models free from cardiac disease, presumably due to the lack of ECM deposition in the young heart. However, exercise has well-reported antifibrotic properties in young models of heart disease that are characterized by elevated fibrotic deposition such as after myocardial infarction (52). Although the mechanisms by which exercise attenuates fibrosis after cardiac injury are not fully clear, the authors posited that an attenuated inflammatory response with exercise likely reduced fibrotic deposition. Indeed, attenuation of the inflammatory response is linked to antifibrotic outcomes of exercise in other instances of cardiac injury (53) and suggests that the mechanisms for reversal or attenuation of fibrosis are intact in the young heart, albeit not activated until administration of a profibrotic stress. Whether these molecular signals for attenuation of fibrosis in the young heart overlap with those that regulate fibrosis in the aged heart is not yet clear. Delineating these pathways by age remains an important focus for future research efforts.

Integration of Hypertrophy, Fibrosis, and Cardiac Function

Exercise-induced cardiac remodeling is the ultimate outcome of both beneficial structural and functional changes in the heart in response to regular exercise training. For example, LV hypertrophy is strongly linked to and likely largely responsible for improved systolic function with exercise training in the young heart. To this end, the lack of hypertrophic remodeling with exercise training in the aged heart may be responsible for diminished improvements in SV and systolic function. However, as discussed previously, interventions that promote cardiovascular health and slow aging also seem to result in regression of LV mass, perhaps suggesting that hypertrophy is not a requirement for improvements in cardiac function or overall cardiac health. The mechanisms of cardiac mass regression are of interest, not only for the aging heart but also for models of cardiac disease that are characterized by pathological hypertrophy. The mechanisms of loss of cardiac mass are not yet clear but could be due to regression of myocyte size or attenuation of ECM deposition. As discussed previously, loss of myocytes with age results in both reactive hypertrophy and replacement fibrosis. Therefore, if exercise attenuates myocyte loss, it may both attenuate/reverse hypertrophy and fibrotic remodeling, thus regressing cardiac mass. Blood pressure also directly regulates cardiac mass, with elevated afterload such as with age-associated hypertension causing hypertrophy. To date, few studies have adequately addressed the blood pressure–lowering effects of exercise; thus, it remains unclear if attenuation of age-associated LV afterload is sufficient to stimulate cardiac mass regression. To begin to address some of these challenges in dissecting cardiac morphological from physiological remodeling, multifaceted approaches that take into consideration physiological, molecular, and morphological outcomes are warranted.

In the work discussed in the scope of this review, changes in fibrosis were often linked to improved relaxation. However, in several cases, changes in fibrosis were independent from diastolic function and vice versa. For example, aged rats demonstrated improved collagen accumulation likely because of enhanced breakdown of ECM in response to HIIT; however, diastolic function was not improved (50). ECM accumulation is strongly linked to LV stiffness (47). However, stiffness is also regulated by the myofilament. Relaxation is composed of a passive and active process and is dependent on the properties of the myofilament. Diastolic function therefore integrates sarcomeric function, extracellular coupling, along with noncardiac contributions from the vascular system. Myofilament-specific adaptations occur during aging and in response to exercise. Furthermore, the impact of exercise on myofilament adaptations differs in aged versus young hearts. For example, age-associated deficits in relaxation are in part due to attenuated sarcoplasmic reticulum Ca^{2+}ATPase activity and prolongation of the calcium transient. These age-dependent alterations of calcium signaling are reversible by chronic exercise training. This finding is interesting given that the sarcoplasmic reticulum does not seem to respond to exercise training in young hearts (reviewed in (54)). Thus, it is clear that the mechanisms by which exercise is cardioprotective in the young and aged hearts are not similar. Identification of the underpinnings by which these outcomes differ is of great interest.

CONSIDERATIONS FOR AGE-SPECIFIC EXERCISE-INDUCED CARDIAC REMODELING

Exercise Intensity and Modality in the Young and Aged

In nearly all studies discussed in this review, aged models exercised at lower intensities than young. Lower exercise intensities are not unexpected, given age-related declines in maximum cardiorespiratory fitness and that voluntary physical activity declines with age. However, few investigations have directly compared responses of the young and aged heart to exercise, and where these studies exist, matching for exercise intensity is difficult. Even in cases when intensity was matched such as in young and aged treadmill-trained rats, cardiac hypertrophy and activation of protective molecular signaling differed by age (55). Emerging work suggests that exercise-induced cardiac hypertrophy and systolic function are intensity dependent (35) at least in young animals. This notion of the importance of intensity is supported by data suggesting that, although moderate-intensity aerobic exercise seems not to largely affect systolic function in older adults (29,56), HIIT imparts systolic benefits, with previously sedentary older adults demonstrating improvements in LV EF after 8 wk of training (57). These data suggest that future efforts should assess whether exercise could elicit more profound outcomes if aged animals were forced to exercise at higher intensities.

Further complicating age-specific cardiac adaptations are differences between forced treadmill and voluntary wheel running, with some preclinical models performing well in one type of training compared with the other. We were unable to find reports comparing these two commonly used preclinical exercise

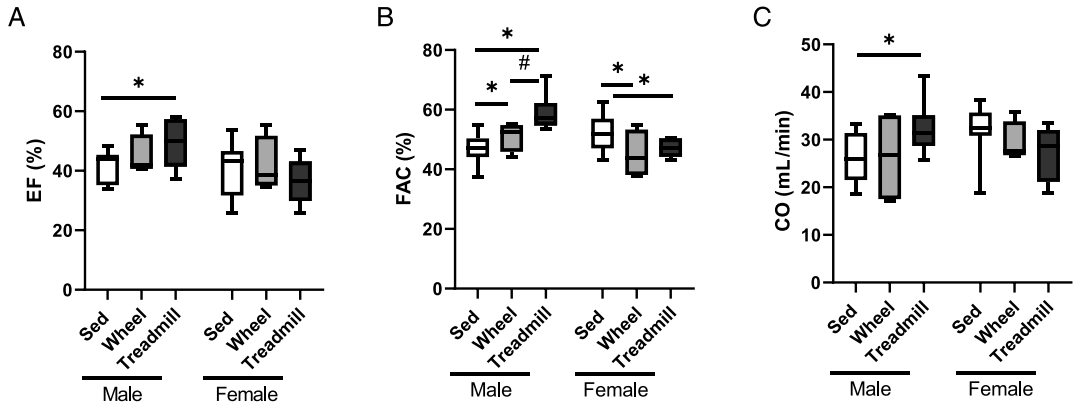

Figure 2. Changes in cardiac function in aged mice in response to voluntary wheel running or forced treadmill training. A. Treadmill running improved ejection fraction (EF) in aged male mice. B. Treadmill and wheel running improved fractional area change (FAC) in aged male mice, with treadmill training more robustly improving FAC. In female mice, wheel running and treadmill running both resulted in lower FAC. C. Improved cardiac output (CO) in aged male mice in response to treadmill training. Eighteen-month old C57Bl6 mice underwent 3 wk of voluntary wheel running or forced treadmill training. Treadmill training occurred in the dark period between 7 p.m. and 8 p.m. Training followed a ramped protocol, with increasing speed and time of exercise on a fixed incline treadmill. Sed, sedentary; Treadmill, forced treadmill exercise; Wheel, voluntary wheel running. *$P < 0.05$, sed versus exercise group within sex. #$P < 0.05$, wheel versus treadmill within sex. Data were analyzed by one-way analysis of variance. Bruns DR, Unpublished data, 2022.

modalities with respect to cardiac remodeling, and definitely not in an aged model where low engagement of aged males in voluntary wheel running is significant. However, we recently compared cardiac function by echocardiography in 18-month-old mice that underwent 4 wk of voluntary wheel running or forced exercise training by ramped treadmill protocol (Bruns DR, unpublished data, 2022). Treadmill training in aged males imparted larger changes in systolic function as evidenced by higher EF, FAC, and CO — effects that were either less robust or not improved with wheel running (Figs. 2A–C). Given the low voluntary wheel-running distances in aged male mice (1 km per night), these findings are not surprising. The low engagement of aged males in voluntary exercise suggests that future work that aims to understand exercise-induced cardiac remodeling in the aged heart must do so with careful selection of exercise intensity and modality.

Sex and Gender Differences in the Young and Aged

Although not a primary focus of the current review, both clinical and preclinical reports demonstrate clear sex differences

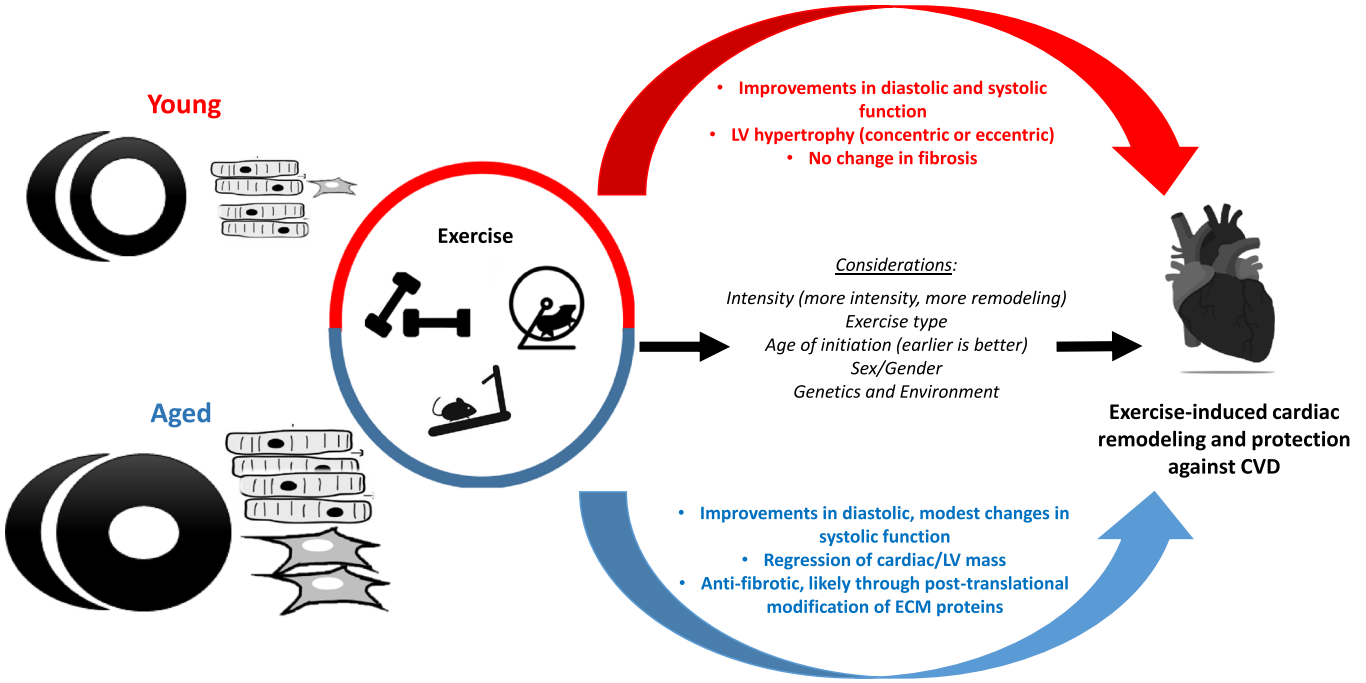

Figure 3. Exercise-induced cardiac remodeling differs between young and aged hearts. The aged heart is hypertrophic and fibrotic compared with the young, with impaired systolic reserve and diastolic function. In response to exercise training, young hearts undergo hypertrophy with improvements in systolic and diastolic functions. Aged hearts do not undergo hypertrophic remodeling but demonstrate regression of fibrosis with minimal changes in cardiac function. Sex/gender, genetics, and factors such as exercise intensity, type, and age of initiation all likely contribute to the different mechanisms of exercise-induced cardiac remodeling in the young and old hearts. Elucidation of these age-specific mechanisms is warranted to facilitate the prescription of exercise as cardiovascular medicine.

in exercise-induced cardiac remodeling. Importantly and in line with similar exercise physiology, sex differences in preclinical models often reflect the same differences in human models. For example, in humans (46) and in rodents (47), females generally undergo more pronounced exercise-induced LV hypertrophy compared with males, even when matched for level of activity, which is typically higher in female animals. Sex differences in cardiac aging also are significant (58) and likely also contribute to differences between sexes in response to exercise. In aged rats, voluntary wheel running elicited better systolic and diastolic improvements in males compared with females, which the authors posited was due to more dramatic deterioration of cardiac function in males with advanced age (6). Historically, sex differences in exercise-induced cardiac remodeling have been attributed to estrogen — a conclusion largely based on the robust cardioprotection afforded by estrogen (reviewed in (48)). However, estrogen likely does not account for all mechanisms of sex-specific cardiac remodeling (59), particularly given the persistence of sex differences into advanced age when estrogen levels decrease with human menopause or cessation of rodent estrous cycling (60). Taken together, sex differences are clearly important in exercise-induced cardiac remodeling, both in the aged and young heart, likely because of complex interactions between genetic, hormonal, and environmental factors.

Timing of Exercise for Cardioprotection

Although exercise is cardioprotective at any age, several lines of evidence suggest that early in life exercise is better than initiation later in life (1). Changes in age-related LV stiffness begin around midlife at 55 yr of age. If training begins around this time, exercise can prevent the increase in cardiac stiffness attributable to sedentary aging (61), unlike similar training programs administered later in life that do not improve LV stiffness (29). Master athletes who trained for the majority of their adult life had LV compliance that was indistinguishable from young controls (44), again suggesting that early or lifelong exercise slows cardiac aging and may permit more robust physiological adaptations than when initiated later in life. Age-related declines in diastolic dysfunction can be attenuated by voluntary wheel running in mice, with differences in sedentary and running animals evident by the second quarter of the lifespan (10 months of age). The authors posited that an early critical period is optimal for exercise-induced anatomical and physiological remodeling (21), given the timing of age-associated declines in activity and cardiac function. Why late in life exercise is less robust than earlier interventions is not clear but may be due to age-related cardiac changes like hypertrophy and fibrosis that become difficult to overcome at advanced age or activation of different molecular signals. The aged myocardium displays a diminished response to pathological hypertrophic stimuli (14) and is well characterized to be desensitized to adrenergic stimulation, suggesting that the aged heart may lose sensitivity to external stimuli. However, this hypothesis does not yet have consensus. Given the paucity of work that has directly compared how the young and aged hearts respond to exercise, the identification of the mechanisms that contribute to age-specific remodeling is an area ripe for research.

CONCLUSIONS

Regular exercise training improves cardiovascular fitness, is undoubtedly protective against cardiovascular disease, and slows cardiac aging if initiated early in life. In the young heart, physiological hypertrophy and concomitant improved systolic and diastolic functions are well described. These adaptations to exercise training, however, are not mirrored in the aged heart (Fig. 3). Although regular exercise improves cardiorespiratory fitness, slows cardiac aging, and lowers the risk for cardiovascular disease, in the setting of aging, exercise results in regression of LV mass, attenuation of fibrosis, and modest improvements in diastolic and systolic functions, which appear to be largely dictated by the intensity of and age at exercise initiation. Despite the significance of exercise as cardiovascular medicine, the mechanisms by which the young and aged hearts benefit from exercise training are far from clear. We suggest that elucidation of age-specific mechanisms for exercise-induced cardiac remodeling will facilitate the use of exercise as cardiac medicine for patients of all ages.

Acknowledgments

The authors thank Musharraf Yusifova for technical assistance.
This work was supported by K01 AG058810-A1 (D.R.B.) and Wyoming INBRE 2P20GM103432.
The authors declare no conflicts of interest.

References

1. Carrick-Ranson G, Sloane NM, Howden EJ, et al. The effect of lifelong endurance exercise on cardiovascular structure and exercise function in women. *J. Physiol.* 2020; 598:2589–605.
2. Forman DE, Manning WJ, Hauser R, Gervino EV, Evans WJ, Wei JY. Enhanced left ventricular diastolic filling associated with long-term endurance training. *J. Gerontol.* 1992; 47(2):M56–8.
3. Weiner RB, Baggish AL. Exercise-induced cardiac remodeling. *Prog. Cardiovasc. Dis.* 2012; 54(5):380–6.
4. *ACSM's Exercise Management for Persons with Chronic Diseases and Disabilities*. 4th Edition. Champaign (IL): Human Kinetics; 2016.
5. Boyle AJ, Shih H, Hwang J, et al. Cardiomyopathy of aging in the mammalian heart is characterized by myocardial hypertrophy, fibrosis and a predisposition towards cardiomyocyte apoptosis and autophagy. *Exp. Gerontol.* 2011; 46(7):549–59.
6. Gazoti Debessa CR, Mesiano Maifrino LB, Rodrigues de Souza R. Age related changes of the collagen network of the human heart. *Mech. Ageing Dev.* 2001; 122(10):1049–58.
7. Cheng S, Xanthakis V, Sullivan LM, et al. Correlates of echocardiographic indices of cardiac remodeling over the adult life course: longitudinal observations from the Framingham Heart Study. *Circulation.* 2010; 122(6):570–8.
8. Unverferth DV, Baker PB, Arn AR, Magorien RD, Fetters J, Leier CV. Aging of the human myocardium: a histologic study based upon endomyocardial biopsy. *Gerontology.* 1986; 32(5):241–51.
9. Capasso JM, Palackal T, Olivetti G, Anversa P. Severe myocardial dysfunction induced by ventricular remodeling in aging rat hearts. *Am. J. Physiol.* 1990; 259(4 Pt 2):H1086–96.
10. Eghbali M, Eghbali M, Robinson TF, Seifter S, Blumenfeld OO. Collagen accumulation in heart ventricles as a function of growth and aging. *Cardiovasc. Res.* 1989; 23(8):723–9.
11. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N. Engl. J. Med.* 2002; 346(11):793–801.
12. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation.* 2003; 108(13):1554–9.
13. Lightfoot JT, DE Geus EJC, Booth FW, et al. Biological/genetic regulation of physical activity level: consensus from GenBioPAC. *Med. Sci. Sports Exerc.* 2018; 50(4):863–73.
14. Yusifov A, Chhatre VE, Zumo JM, et al. Cardiac response to adrenergic stress differs by sex and across the lifespan. *Geroscience.* 2021; 43:1799–813.
15. Woulfe KC, Bruns DR. From pediatrics to geriatrics: mechanisms of heart failure across the life-course. *J. Mol. Cell. Cardiol.* 2019; 126:70–6.

16. No MH, Heo JW, Yoo SZ, et al. Effects of aging and exercise training on mitochondrial function and apoptosis in the rat heart. *Pflugers Arch.* 2020; 472(2):179–93.
17. Darband SG, Sadighparvar S, Yousefi B, Kaviani M, Mobaraki K, Majidinia M. Combination of exercise training and L-arginine reverses aging process through suppression of oxidative stress, inflammation, and apoptosis in the rat heart. *Pflugers Arch.* 2020; 472(2):169–78.
18. Roh JD, Houstis N, Yu A, et al. Exercise training reverses cardiac aging phenotypes associated with heart failure with preserved ejection fraction in male mice. *Aging Cell.* 2020; 19:e13159.
19. Roh J, Rhee J, Chaudhari V, Rosenzweig A. The role of exercise in cardiac aging: from physiology to molecular mechanisms. *Circ. Res.* 2016; 118(2): 279–95.
20. Fuller KNZ, Thyfault JP. Barriers in translating preclinical rodent exercise metabolism findings to human health. *J. Appl. Physiol. (1985).* 2021; 130(1): 182–92.
21. Turner MJ, Chavis MN, Turner TH. Enhanced diastolic filling performance with lifelong physical activity in aging mice. *Med. Sci. Sports Exerc.* 2013; 45(10):1933–40.
22. Jerlhag E, Egecioglu E, Dickson SL, Douhan A, Svensson L, Engel JA. Ghrelin administration into tegmental areas stimulates locomotor activity and increases extracellular concentration of dopamine in the nucleus accumbens. *Addict. Biol.* 2007; 12(1):6–16.
23. Brooks GA, Fahey Thomas A, Baldwin KM. *Exercise Physiology: Human Bioenergetics and Its Applications*. Maidenhead (UK): McGraw Hill; 2005.
24. Iemitsu M, Miyauchi T, Maeda S, et al. Exercise training improves cardiac function-related gene levels through thyroid hormone receptor signaling in aged rats. *Am. J. Physiol. Heart Circ. Physiol.* 2004; 286(5):H1696–705.
25. Borzsei D, Priksz D, Szabo R, et al. Exercise-mitigated sex-based differences in aging: from genetic alterations to heart performance. *Am. J. Physiol. Heart Circ. Physiol.* 2021; 320(2):H854–66.
26. Stratton JR, Levy WC, Cerqueira MD, Schwartz RS, Abrass IB. Cardiovascular responses to exercise. Effects of aging and exercise training in healthy men. *Circulation.* 1994; 89(4):1648–55.
27. Brenner DA, Apstein CS, Saupe KW. Exercise training attenuates age-associated diastolic dysfunction in rats. *Circulation.* 2001; 104(2):221–6.
28. Levy WC, Cerqueira MD, Abrass IB, Schwartz RS, Stratton JR. Endurance exercise training augments diastolic filling at rest and during exercise in healthy young and older men. *Circulation.* 1993; 88(1):116–26.
29. Fujimoto N, Prasad A, Hastings JL, et al. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. *Circulation.* 2010; 122(18):1797–805.
30. Fujimoto N, Hastings JL, Carrick-Ranson G, et al. Cardiovascular effects of 1 year of alagebrium and endurance exercise training in healthy older individuals. *Circ. Heart Fail.* 2013; 6(6):1155–64.
31. Haykowsky M, McGavock J, Vonder Muhll I, et al. Effect of exercise training on peak aerobic power, left ventricular morphology, and muscle strength in healthy older women. *J. Gerontol. A Biol. Sci. Med. Sci.* 2005; 60(3):307–11.
32. Atchley AE Jr., Douglas PS. Left ventricular hypertrophy in athletes: morphologic features and clinical correlates. *Cardiol. Clin.* 2007; 25(3):371–82, v.
33. Schuttler D, Clauss S, Weckbach LT, Brunner S. Molecular mechanisms of cardiac remodeling and regeneration in physical exercise. *Cells.* 2019; 8(10):1128.
34. Neri Serneri GG, Boddi M, Modesti PA, et al. Increased cardiac sympathetic activity and insulin-like growth factor-I formation are associated with physiological hypertrophy in athletes. *Circ. Res.* 2001; 89(11):977–82.
35. Kemi OJ, Haram PM, Loennechen JP, et al. Moderate vs. high exercise intensity: differential effects on aerobic fitness, cardiomyocyte contractility, and endothelial function. *Cardiovasc. Res.* 2005; 67(1):161–72.
36. Walton RD, Jones SA, Rostron KA, et al. Interactions of short-term and chronic treadmill training with aging of the left ventricle of the heart. *J. Gerontol. A Biol. Sci. Med. Sci.* 2016; 71(8):1005–13.
37. Choi SY, Chang HJ, Choi SI, et al. Long-term exercise training attenuates age-related diastolic dysfunction: association of myocardial collagen cross-linking. *J. Korean Med. Sci.* 2009; 24(1):32–9.
38. Iemitsu M, Maeda S, Jesmin S, Otsuki T, Miyauchi T. Exercise training improves aging-induced downregulation of VEGF angiogenic signaling cascade in hearts. *Am. J. Physiol. Heart Circ. Physiol.* 2006; 291(3):H1290–8.
39. Lai CH, Ho TJ, Kuo WW, et al. Exercise training enhanced SIRT1 longevity signaling replaces the IGF1 survival pathway to attenuate aging-induced rat heart apoptosis. *Age (Dordr.).* 2014; 36(5):9706.
40. Quarles E, Basisty N, Chiao YA, et al. Rapamycin persistently improves cardiac function in aged, male and female mice, even following cessation of treatment. *Aging Cell.* 2020; 19(2):e13086.
41. Wisloff U, Loennechen JP, Currie S, Smith GL, Ellingsen O. Aerobic exercise reduces cardiomyocyte hypertrophy and increases contractility, Ca^{2+} sensitivity and SERCA-2 in rat after myocardial infarction. *Cardiovasc. Res.* 2002; 54(1):162–74.
42. Cui JW, Hong Y, Kuo YM, et al. Voluntary exercise training attenuated the middle-aged maturity-induced cardiac apoptosis. *Life Sci.* 2020; 259:118187.
43. Kwak HB, Song W, Lawler JM. Exercise training attenuates age-induced elevation in Bax/Bcl-2 ratio, apoptosis, and remodeling in the rat heart. *FASEB J.* 2006; 20(6):791–3.
44. Arbab-Zadeh A, Dijk E, Prasad A, et al. Effect of aging and physical activity on left ventricular compliance. *Circulation.* 2004; 110(13):1799–805.
45. Spina RJ, Meyer TE, Peterson LR, Villareal DT, Rinder MR, Ehsani AA. Absence of left ventricular and arterial adaptations to exercise in octogenarians. *J. Appl. Physiol.* 2004; 97(5):1654–9.
46. Meschiari CA, Ero OK, Pan H, Finkel T, Lindsey ML. The impact of aging on cardiac extracellular matrix. *Geroscience.* 2017; 39(1):7–18.
47. Yamamoto K, Masuyama T, Sakata Y, et al. Myocardial stiffness is determined by ventricular fibrosis, but not by compensatory or excessive hypertrophy in hypertensive heart. *Cardiovasc. Res.* 2002; 55(1):76–82.
48. Thomas DP, Cotter TA, Li X, McCormick RJ, Gosselin LE. Exercise training attenuates aging-associated increases in collagen and collagen crosslinking of the left but not the right ventricle in the rat. *Eur. J. Appl. Physiol.* 2001; 85(1–2):164–9.
49. Wright KJ, Thomas MM, Betik AC, Belke D, Hepple RT. Exercise training initiated in late middle age attenuates cardiac fibrosis and advanced glycation end-product accumulation in senescent rats. *Exp. Gerontol.* 2014; 50:9–18.
50. Guzzoni V, Marqueti RC, Durigan JLQ, et al. Reduced collagen accumulation and augmented MMP-2 activity in left ventricle of old rats submitted to high-intensity resistance training. *J. Appl. Physiol.* 2017; 123(3):655–63.
51. Kwak HB, Kim JH, Joshi K, Yeh A, Martinez DA, Lawler JM. Exercise training reduces fibrosis and matrix metalloproteinase dysregulation in the aging rat heart. *FASEB J.* 2011; 25(3):1106–17.
52. Puhl SL, Muller A, Wagner M, et al. Exercise attenuates inflammation and limits scar thinning after myocardial infarction in mice. *Am. J. Physiol. Heart Circ. Physiol.* 2015; 309(2):H345–59.
53. Liao Z, Li D, Chen Y, et al. Early moderate exercise benefits myocardial infarction healing via improvement of inflammation and ventricular remodelling in rats. *J. Cell. Mol. Med.* 2019; 23(12):8328–42.
54. Moore RL, Korzick DH. Cellular adaptations of the myocardium to chronic exercise. *Prog. Cardiovasc. Dis.* 1995; 37(6):371–96.
55. Starnes JW, Taylor RP, Park Y. Exercise improves postischemic function in aging hearts. *Am. J. Physiol. Heart Circ. Physiol.* 2003; 285(1):H347–51.
56. Spina RJ, Ogawa T, Kohrt WM, Martin WH 3rd, Holloszy JO, Ehsani AA. Differences in cardiovascular adaptations to endurance exercise training between older men and women. *J. Appl. Physiol. (1985).* 1993; 75(2): 849–55.
57. Hwang CL, Yoo JK, Kim HK, et al. Novel all-extremity high-intensity interval training improves aerobic fitness, cardiac function and insulin resistance in healthy older adults. *Exp. Gerontol.* 2016; 82:112–9.
58. Dworatzek E, Baczko I, Kararigas G. Effects of aging on cardiac extracellular matrix in men and women. *Proteomics Clin. Appl.* 2016; 10(1):84–91.
59. Konhilas JP, Chen H, Luczak E, et al. Diet and sex modify exercise and cardiac adaptation in the mouse. *Am. J. Physiol. Heart Circ. Physiol.* 2015; 308(2): H135–45.
60. Yusifov A, Chhatre VE, Koplin EK, et al. Transcriptomic analysis of cardiac gene expression across the life course in male and female mice. *Physiol. Rep.* 2021; 9(13):e14940.
61. Howden EJ, Sarma S, Lawley JS, et al. Reversing the cardiac effects of sedentary aging in middle age-a randomized controlled trial: implications for heart failure prevention. *Circulation.* 2018; 137(15):1549–60.