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Effects of Moderate-Intensity Treadmill Training on Cardiac Mitochondrial Mitophagy and Dynamics in Young and Aged Wistar Rats

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Abstract

Background: Cardiac aging is closely associated with mitochondrial dysfunction and impaired quality control mechanism. Exercise has been shown to modulate mitochondrial homeostasis, however, its effects on cardiac mitophagy and mitochondrial dynamics during aging remain unclear. This study investigated the effects of moderate-intensity treadmill training on mitochondrial maintenance-related gene expression in the hearts of young and aged Wistar rats.

Methods: Young and aged rats were divided into four groups: young control, young exercise, aged control, and aged exercise (n=6 per group). Exercise groups performed treadmill running at 20 m/min for 30 minutes/day, 5 days/week for 8 weeks. Cardiac gene expression levels of *Pink1*, *Parkin*, *Mfn1, Mfn2, Opa1, Drp1,* and *Fis1* were analyzed using semi-quantitative polymerase chain reaction (PCR). Data were analyzed using one-way ANOVA or Kruskal–Wallis test followed by appropriate post hoc analyses.

Results: Exercise significantly increased *Mfn2* expression in aged exercise rats compared with aged controls (p=0.0294), suggesting partial restoration of age-related decline. Expression of *Mfn1* and *Drp1* varied among groups but showed no significant pairwise differences. Expression levels of *Opa1, Fis1, Pink1,* and *Parkin* remained unchanged. These results indicate that moderate exercise selectively enhances mitochondrial fusion capacity while maintaining balanced fission and basal mitophagy activity.

Conclusions: Moderate-intensity treadmill training promotes mitochondrial fusion-related adaptation in aging cardiac tissue. Regular moderate exercise may represent a potential non-pharmacological strategy to support mitochondrial function and mitigate cardiovascular aging.

Keywords: Aging, exercise training, gene expression, mitophagy, mitochondrial dynamics

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Introduction

Proper mitochondrial quality control is essential for maintaining cardiac function, particularly during aging. This process relies on two key mechanisms: mitochondrial dynamics, involving continuous fusion and fission, and mitophagy, which selectively removes damaged mitochondria.[1,2] Mitochondrial fusion is regulated by

Mitofusin-1 (*Mfn1*), Mitofusin-2 (*Mfn2*), and Optic Atrophy-1 (*Opa1*), all of which play critical roles in maintaining mitochondrial integrity and cardiac health.[3,4] On the other hand, mitochondrial fission is primarily mediated by Dynamin-related protein-1 (*Drp1*), whose deficiency has been associated with severe cardiac aging phenotype.[5]

Mitophagy serves as an essential quality control mechanism by eliminating dysfunctional mitochondria to preserve cellular homeostasis. This process is commonly regulated through the *PINK1*/*Parkin* pathway, in which *PINK1* detects mitochondrial damage and recruits *Parkin* to label impaired mitochondria for degradation.[1] However, in aging hearts, mitophagy efficiency declines, leading to the accumulation of enlarged and dysfunctional mitochondria that are less efficiently cleare.[2,6]

Endurance exercise has been shown to modulate mitochondrial dynamics and improve mitochondrial quality control in cardiac tissue.[7] Exercise promotes a shift toward mitochondrial fusion and enhances network connectivity. For instance, aerobic exercise has been reported to increase *Opa1* and *Drp1* expression while suppressing excessive *Mfn2* in heart failure models.[8] In contrast, studies in healthy rodents have shown increased expression of *Mfn1* and *Mfn2*, accompanied by reduced *Drp1* and *Opa1* levels, reflecting a more fused mitochondrial network.[9] Mitochondrial fission is also regulated by Fission protein 1 (*Fis1*), which acts as an outer mitochondrial membrane receptor that recruits *Drp1* to initiate mitochondrial division.[10]

In addition to influencing mitochondrial dynamics, exercise can stimulate mitophagy and autophagy pathways under some conditions. Experimental study in rat has revealed that short-term treadmill exercise activates the heart's autophagy machinery, as seen by rises in LC3-II/I and BNIP3 levels, signaling more active mitochondrial turnover.[11] The *PINK1*/*Parkin* pathway may also be involved, as endurance exercise has been shown to increase *Parkin* expression and its translocation to mitochondria in skeletal muscle.[12] However, the exact contribution of *PINK1*/*Parkin*-mediated mitophagy in exercise-induced cardiac adaptation remains unclear. Emerging evidence suggests that alternative pathways, including BNIP3- and FUNDC1-mediated mitophagy, as well as basal mitophagy, may compensate under certain conditions.[2] Although exercise is widely known to support mitochondrial health, its specific effects on cardiac mitochondrial remodeling and mitophagy during aging remain to be fully clarified.

Therefore, this study aimed to investigate the effects of moderate-intensity exercise on gene expression related to mitochondrial dynamics and mitophagy in the aging heart. The genes examined included those involved in mitophagy (*Pink1*/*Parkin*), mitochondrial fusion (*Mfn1, Mfn2, Opa1*), and mitochondrial fission (*Drp1, Fis1*). It was hypothesized that aging alters the expression of these genes in cardiac tissue, and that regular moderate-intensity exercise may attenuate these age-related changes.

Methods

This experimental study used male Wistar rats divided in two age groups: young (12 weeks) and aged (80 weeks). Each age group was further allocated into sedentary control and exercise groups (n=6 per group, total n=24), resulting in four group: young control, young exercise, aged control, and aged exercise. Rats in the exercise groups underwent a moderate-intensity treadmill training program for 8 weeks, while control groups remained sedentary and were placed on the treadmill without exercise exposure. The exercise protocol consisted of running at a speed of 20 m/min for 30 minutes per day, 5 days per week.[13,14] This protocol was designed to represent moderate-intensity exercise without inducing excessive fatigue or injury. Aged rats were closely monitored throughout the intervention, and all animals completed the training without adverse events.

The study was conducted from January to September 2024 at the Maranatha Biomedical Research Laboratory and Animal Laboratory, and the Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Kristen Maranatha (Ethics No. 127/KEP/VIII/2024).

At the end of the intervention, rats were euthanized, and cardiac tissues were rapidly harvested. Left ventricular tissue was immediately frozen in liquid nitrogen and stored at –80 °C until analysis. Total RNA was then extracted using GENEzol reagent (GZR200, Geneaid Biotech Ltd, Taiwan) according to the manufacturer's instructions, and RNA quality was assessed using UV spectrophotometry.

Gene expression analysis was performed using semi-quantitative polymerase chain

Table 1 Primers Used in Semi-Quantitative PCR

Gene	Sense Primer (5′–3′)	Antisense Primer (5′–3′)	Size (bp)	Ref
Pink1	TGCAATGCCGCTGTGTATGA	TCTGCTCCCTTTGAGACGAC	113	15
Parkin	CCAAACCGGATGAGTGGTGAGTGC	ACACGGCAGGGAGTAGCCAAGTTG	303	16
Mfn1	CTCCTGTAATCTTGCCTG	ATCGGATCTTTTTTGTTTCAGC	116	17
Mfn2	TCAGTAGCCAATCTGGACCT	TCTCTTGGATGTAGGCCCCC	277	15
Opa1	GATGACACGCTCTCCAGTGAAG	CTCCGGGGCTAACAGTACAACC	179	18
Drp1	CGCTGATCCCGGTCATCAAT	ACTCCATTTTCTTCTCCTGTTGT	247	15
Fis1	AAAGAGGAGCAGCGGGATTA	TGGGGCTCAGTCTGTAACAG	110	15
Gapdh	GTTACCAGGGCTGCCTTCTC	GATGGTGATGGGTTTCCCGT	177	19

Note: Gapdh was used as the internal control.

reaction (PCR). The genes analyzed included those related to mitophagy (*Pink1, Parkin*), mitochondrial fusion (*Mfn1, Mfn2, Opa1*), and mitochondrial fission (*Drp1, Fis1*). Gene-specific primers were designed based on published rat sequences and validated for specificity (Table 1). *Gapdh* was used as the housekeeping gene for normalization. PCR amplification was carried out using a thermal cycler under optimized conditions (30–35 cycles) to ensure linear amplification.

PCR products were separated by electrophoresis on 2% agarose gels and stained with SYBR Safe (Invitrogen, USA). Band intensities were quantified using ImageJ software and normalized to *Gapdh* expression. Results were expressed as relative expression ratios of target genes to the housekeeping gene.

Data were presented as mean ± standard error of the mean (SEM). Statistical analysis was performed using GraphPad Prism version 10.0 (GraphPad Software, San Diego, CA, USA). Normality and homogeneity of variance were assessed prior to analysis. For normally distributed data, comparisons among groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. For non-normally distributed data, the Kruskal–Wallis test was applied, followed by Dunn's post hoc test. A p-value <0.05 was considered statistically significant.

Results

After 8 weeks of moderate treadmill training, the relative cardiac mRNA expression of *Pink1* and *Parkin* showed no significant differences among groups (Figure 1). *Pink1* expression did not differ significantly between young and

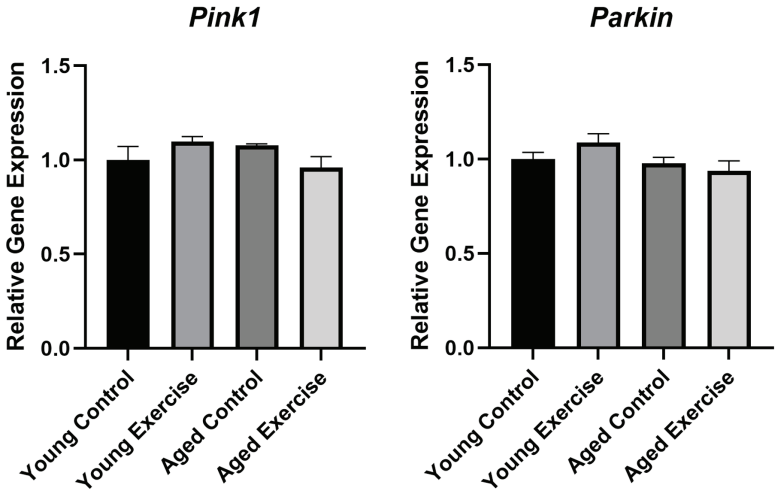

Figure 1 Cardiac mRNA Expression of *PINK1* and *Parkin* in Young and Aged Rats Following 8 Weeks of Moderate-Intensity Treadmill Training

Note: No significant differences were observed among groups. Data are presented as mean ± standard error of the mean (SEM).

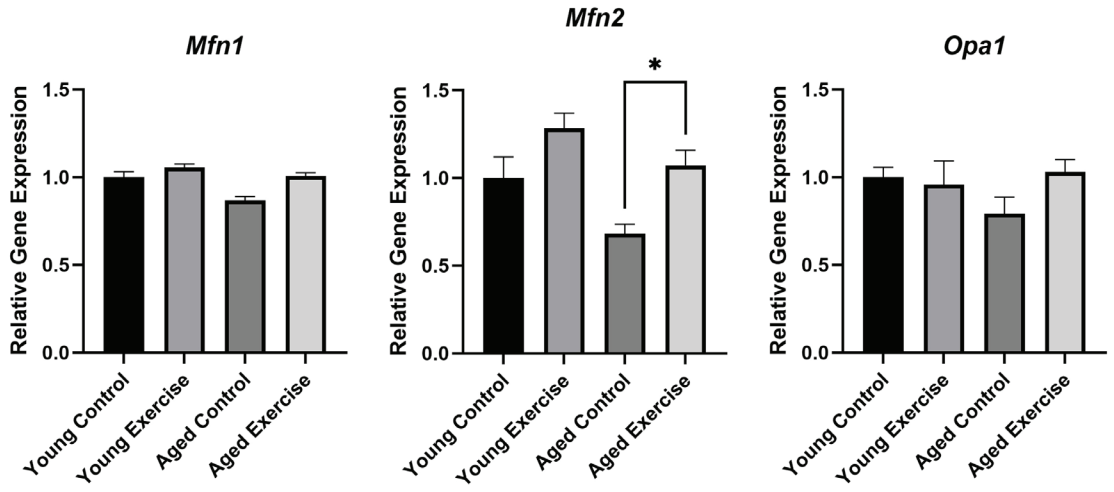

Figure 2 Cardiac mRNA Expression of Mitochondrial Fusion Genes (*Mfn1, Mfn2,* and *Opa1)* in Young and Aged Rats After 8 Weeks of Moderate-Intensity Treadmill Training

Note: *Mfn1* expression showed variability among groups but no significant pairwise differences. *Mfn2* expression was significantly higher in old exercised rats compared with aged controls, whereas *Opa1* expression did not differ significantly among groups. Data are presented as mean ± standard error of the mean (SEM) (n=6 per group). *p<0.05.

aged rats (p=0.5351) and was not affected by exercise. Similarly, *Parkin* expression remained comparable across all groups (p=0.1248), suggesting that moderate treadmill exercise was insufficient to significantly modify the expression of key mitophagy genes in cardiac tissue.

Expression levels of genes related to mitochondrial fusion are presented in Figure 2. A significant overall difference in *Mfn1* expression was observed among groups based on the Kruskal–Wallis test (p=0.0057). However, post hoc analysis showed no significant pairwise differences between the young control and young exercise groups or between the aged control and aged exercise groups. Thus, although variability existed across groups, there was no clear effect of exercise or age that could be confirmed for *Mfn1*.

In contrast, *Mfn2* expression exercise was significantly higher in the aged exercise group compared to the aged control group (p=0.0294), indicating that regular moderate exercise partially restored the age-related decline in *Mfn2* expression. No significant differences were observed in *Opa1* expression among groups (p=0.1477), suggesting that inner membrane fusion remained relatively stable under this exercise regimen. Overall, these findings indicated that moderate-intensity treadmill training mainly affects *Mfn2*, enhancing mitochondrial fusion capacity in the aging heart, while *Mfn1* and *Opa1* remain largely unchanged.

As shown in Figure 3, eight weeks of moderate treadmill training influenced the expression of mitochondrial fission genes. Kruskal–Wallis analysis revealed a significant overall difference in *Drp1* expression among groups (p=0.0155); however, post hoc comparisons showed no significant differences between the young control and young exercise groups, nor between aged control and aged exercise groups. This indicates that although *Drp1* expression varied across groups, the exercise intervention did not significantly alter *Drp1* levels within each age group. In contrast, *Fis1* expression did not differ significantly among any groups (p=0.3472), suggesting that this outer membrane fission-related gene was relatively stable regardless of age or exercise condition.

Discussion

This study demonstrated that 8 weeks of moderate-intensity treadmill exercise did not significantly alter *Pink1* and *Parkin* gene expression in the cardiac tissue of either young or aged rats. These findings suggest that moderate aerobic exercise does not upregulate the canonical *PINK1/Parkin*-mediated mitophagy pathway under physiological

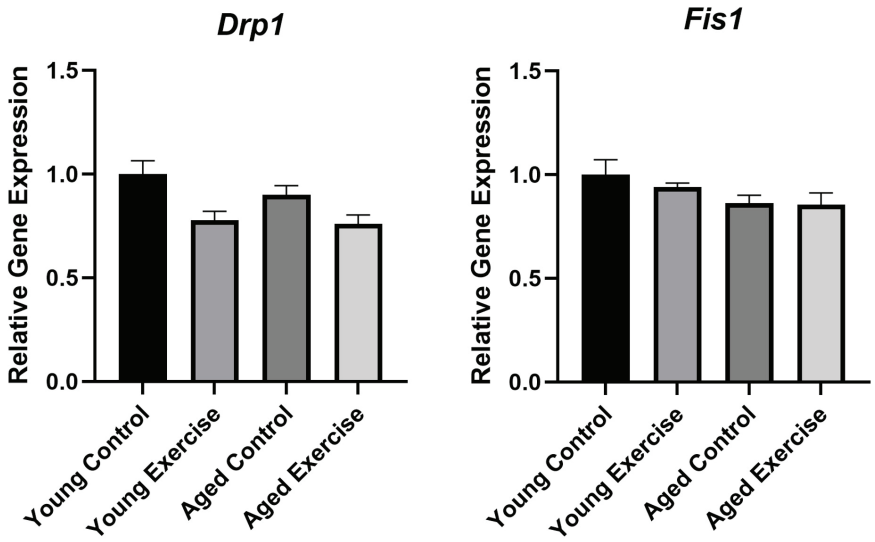

Figure 3 Cardiac mRNA Expression of Mitochondrial Fission Genes (*Drp1 and Fis1)* in Young and Aged Rats Following 8 Weeks of Moderate-Intensity Treadmill Training.

Note: Drp1 expression showed variability among groups but no significant pairwise differences within either age group. Fis1 expression did not differ significantly among groups. Data are presented as mean ± standard error of the mean (SEM) (n = 6 per group).

conditions.

This finding provides important insight into the regulation of mitophagy in the heart, particularly in the context of aging. *PINK1* and *Parkin* together drive the canonical pathway of selective mitochondrial autophagy: *PINK1* accumulates on the outer membrane of damaged mitochondria and recruits Parkin to initiate their clearance.[20] One might expect that stimuli enhancing mitochondrial turnover, such as exercise, would increase *Pink1/Parkin* expression. Indeed, under certain conditions, exercise has been shown to enhance *PINK1/Parkin* signaling. For example, in a myocardial infarction model, exercise training, especially resistance exercise via the Irisin pathway, robustly activated *PINK1/Parkin*-mediated mitophagy in in cardiac tissue.[21] Similarly, very intense or exhaustive exercise has been reported to transiently increase mitophagy markers in mice.[21] However, our findings suggest that moderate-intensity endurance exercise in otherwise healthy rats imposes a stimulus that is insufficient to induce upregulation of *Pink1* or *Parkin* gene expression, at least in a chronic setting. This could imply that the basal mitophagy capacity is adequate to manage exercise-induced mitochondrial stress. Alternatively, the beneficial effects of exercise may be mediated primarily through improvements in mitochondrial quality, such as enhanced biogenesis, fusion, and fission, rather than through activation of the *PINK1/Parkin*-dependent damage-control pathway.

In this study, 8 weeks of moderate-intensity treadmill training elicited distinct changes in genes governing mitochondrial dynamics in the left ventricle. Notably, exercise significantly upregulated the fusion-related mitofusin genes. Among the fusion genes, only *Mfn2* showed a significant response to exercise, specifically in aged rats, where its expression increased compared with aged controls. Although *Mfn1* showed significant overall variability based on Kruskal–Wallis analysis, post hoc testing did not revealsignificant differences within each age group, and *Opa1* expression remained stable. These results indicate that the beneficial effect of moderate exercise on mitochondrial fusion during aging are primarily mediated through *Mfn2*. This observation is consistent with previous reports indicating that endurance exercise enhance cardiac mitochondrial fusion capacity by increasing *Mfn1* and *Mfn2* levels.[22,23] The exercise-induced rise in *Mfn2* is particularly important, as aging hearts are often characterized by reduced *Mfn2* expression.[24] Age-related deficiency of *Mfn2* has been linked to mitochondrial fragmentation and dysfunction in muscle,[22,25] so its partial restoration in aged exercise rats may reflect a protective adaptation against mitochondrial deterioration. Interestingly,

Opa1, which mediates inner mitochondrial membrane fusion, did not change significantly, suggesting that moderate exercise does not uniformly affect all components of the fusion machinery. It is possible that *Opa1* is maintained at adequate levels or regulated post-transcriptionally, which would not be captured at the mRNA level.

Regarding mitochondrial fission, *Drp1* showed overall variation across groups, however, no significant pairwise differences were identified within age groups. Descriptively, *Drp1* expression tended to be lower in aged rats than in young rats, consistent with a potential age-related decline in fission drive, while exercise did not significantly modify this trend. Similarly, *Fis1* expression remained unchanged across all groups. One possible interpretation is that aging myocardium, even with exercise, exhibits a relatively dampened fission response, potentially as an adaptive mechanism to prevent excessive mitochondrial fragmentation. Previous studies have reported mixed findings regarding the effects of aging on mitochondrial fission. Some have shown increased *Drp1* and *Fis1* protein expression with aging, favoring a fragmented mitochondrial phenotype, whereas others have demonstrated preserved or normalized fission following exercise interventions.[22,23,26] In the present study, the non-significant reduction in *Drp1* expression in aged exercise rats may indicate that moderate exercise does not strongly activate fission pathways in aging hearts. Instead, exercise appears to shift the balance toward fusion, as evidenced by the upregulation of *Mfn2*.[9,23] This observation aligns with the concept that exercise helps restore the balance between mitochondrial fusion and fission.[3] For instance, moderate continuous training has been shown to preserve *Mfn2* levels in aged hearts, while higher-intensity exercise may reverse age-related alterations in mitochondrial dynamics protein.[27] By promoting fusion without exacerbating fission, moderate exercise may support a more interconnected mitochondrial network, which is associated with improved oxidative efficiency and cellular resilience.[28]

It is important to recognize that mitochondrial dynamics represent a tightly regulated balance. While excessive fission can impair mitochondrial function, a certain degree of fission is necessary for mitophagy and mitochondrial turnover.[29] *Drp1* plays a critical role in segregating damaged mitochondria for degradation, and its deficiency has been associated with cardiac dysfunction in experimental models.[30] Therefore, the biological significance of reduced *Drp1* expression in aged exercised rats remains unclear. It may reflect a protective adaptation that limits excessive fragmentation, or alternatively, an age-related decline in adaptive fission capacity. In pathological conditions, reduced *Drp1* activity has been linked to impaired mitophagy and increased cardiomyocyte apoptosis.[30] In the present physiological aging model, moderate exercise likely optimizes mitochondrial morphology and connectivity without suppressing essential fission processes. Supporting this notion, previous studies using electron microscopy have shown that exercise can prevent abnormal mitochondrial fragmentation in aged cardiac tissue.[27] Overall, the combination of increased fusion-related gene expression and stable or slightly reduced fission markers suggests that moderate exercise promotes a more integrated and functionally efficient mitochondrial network in the aging heart.

Collectively, these findings provide insight into the mechanisms by which moderate exercise enhances mitochondrial quality control in the aging myocardium. Upregulation of *Mfn2* suggests enhanced mitochondrial fusion, which facilitates the exchange of mitochondrial contents, dilutes damaged components, and helps maintain membrane potential.[29] Increased mitochondrial interconnectivity is also associated with improved oxidative phosphorylation efficiency and resistance to apoptotic signaling.[23] In contrast, excessive fission leads to mitochondrial fragmentation and dysfunction, which are commonly observed in cardiac aging and disease.[3,28,30] The absence of significant changes in *Drp1* and *Opa1* suggests that moderate exercise does not induce a pro-fission state, which may be beneficial in preventing chronic mitochondrial fragmentation. This could be protective, as chronic fragmentation is associated with aging and heart failure.[30] By boosting *Mfn1/Mfn2*, exercise may counteract the aging process, which otherwise tends to downregulate these fusion genes. Furthermore, *Mfn2* has roles beyond fusion, including participation in mitophagy through its interaction with *Parkin* following *PINK1*-mediated phosphorylation.[4] Therefore, increased *Mfn2* expression may enhance the efficiency of mitochondrial quality control, even in the absence of changes in *PINK1* and *Parkin* gene expression. This suggests that exercise may prime the mitochondrial network for efficient turnover under stress conditions.

While these results shed light on molecular adaptations, several limitations should be acknowledged. First, this study assessed gene expression at the mRNA level only, which may not directly reflect protein abundance or functional activity. Second, only one exercise modality and intensity were evaluated; different training intensities or longer durations may produce different molecular responses. Third, functional assessments of cardiac performance and mitochondrial activity were not performed. Future studies incorporating protein-level analyses, functional assays, and evaluation of mitophagy flux are warranted to better elucidate the mechanisms underlying these adaptations. Despite these limitations, the findings are consistent with known physiological benefits of exercise and provide meaningful insight into mitochondrial adaptations in aging.

In conclusion, 8 weeks of moderate-intensity treadmill training promotes favorable adaptations in cardiac mitochondrial quality control, particularly by enhancing mitochondrial fusion while avoiding excessive activation of fission pathways. The upregulation of *Mfn2* suggests a partial reversal of age-related mitochondrial dysfunction, supporting a more fusion-dominant and functionally efficient mitochondrial network. The absence of significant changes in *PINK1, Parkin, Mfn1, Opa1, Drp1*, and *Fis1* indicates that moderate exercise maintains basal mitophagy without activating stress-induced clearance pathways.

Overall, these findings highlight moderate aerobic exercise as an effective non-pharmacological strategy to preserve mitochondrial integrity, sustain energy production, and mitigate oxidative stress in the aging heart. By fine-tuning the balance between mitochondrial fusion and fission, exercise may attenuate key processes underlying cardiac aging and reinforce its role as a cornerstone of cardiovascular health across the lifespan.

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Authors' Contributions
JWG conceived and designed the study, supervised the project, interpreted the data, and led manuscript writing and revision. DHR, BTS, and AAR conducted the experiments, collected and analyzed the data, and contributed to manuscript drafting. RW and YL supervised the research process, provided scientific guidance, and contributed to manuscript revision. HG and RL provided technical expertise, supported experimental design and analysis, and critically revised the manuscript. All authors approved the final version of the manuscript.

Conflict of Interest
The authors declare no conflict of interest.

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Generative AI Disclosure Statement
Generative AI was used solely for grammar correction and language editing. The authors reviewed and approved all content and take full responsibility for the manuscript.

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