Sport Sciences and Health Research

University of Tehran
Faculty of
Physical Education and Sport Science

The impact of different exercise training types on cardiac Vimentin in Wistar male rats

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Article Info

Article type:

Original Article

Article history:

Received: 09 May 2025

Revised: 20 July 2025

Accepted: 15 September 2025

Published online: 01 January 2026

Abstract

Background: Vimentin, a cytoskeletal protein in cardiomyocytes, plays a key role in maintaining structural integrity and transmitting mechanical signals.

Aim: This study aimed to investigate the impacts of resistance training (RT), endurance training (ET), and high-intensity interval training (HIIT) on cardiac vimentin levels in male Wistar rats.

Materials and Methods: Thirty-two male rats (8 weeks old, average weight of 218.6±13.8 grams) were divided into four groups: control, RT, ET, and HIIT. Exercise protocols were implemented for 8 weeks: RT using a vertical ladder with progressive load increases, ET as continuous running at 65–70% of maximal oxygen consumption (VO_2max), and HIIT involving 8-minute intervals at 85–90% VO_2max with recovery periods. Cardiac vimentin levels were assessed via immunofluorescence. Data were analyzed using ANOVA and Tukey's post hoc test.

Results: All exercise training groups showed a significant increase in cardiac vimentin compared to the control group (P=0.0001). The HIIT group exhibited the highest increase, significantly surpassing both ET (P=0.001) and RT (P=0.0001). These results highlight the influence of exercise intensity on vimentin expression.

Conclusion: the findings suggest that exercise training, particularly HIIT, increases cardiac vimentin levels in rats. This increase may represent a structural adaptation in response to exercise-induced mechanical stress. However, given the dual role of vimentin in both physiological and pathological processes, these results should be interpreted with caution Future studies correlating vimentin changes with cardiac function and fibrosis markers are essential to define this response's exact nature.

Keywords: Vimentin, high-intensity interval training, resistance training, endurance training. cardiac adaptation.

Cite this article: Borjian Fard, M., Soori, R., & Mazaheri, Z. (2026). The impact of different exercise training types on cardiac Vimentin in Wistar male rats. *Sport Sciences and Health Research*, 18(1), 84-93.

1. Introduction

The human heart functions as a tireless pump, continuously circulating blood throughout the body. To perform this vital function effectively, the heart relies on the proper structure and function of its specialized cells, called cardiomyocytes. These muscular cells are responsible for contracting and propelling blood, and their health is critical for overall cardiovascular well-being(1).

The cardiac cytoskeleton represents the main structural scaffold of myocytes essential in the regulation of cell shape and mechanical integrity(2). This internal scaffolding comes in three main forms: actin microfilaments, microtubules, and intermediate filaments (IFs)(3). Intermediate filaments are named for their size, which falls between the thinner actin filaments and the thicker microtubules. However, despite their name, intermediate filaments are unique in their structure, behavior, and how they impact the cell compared to the other two types(4).

Unlike the more uniform actin and microtubules, IFs are a diverse group of proteins with specific functions depending on the cell type(5). IF proteins can be categorized into six distinct types based on variations in their rod domain sequence and terminal domain functionalities. These categories exhibit differences in their biochemical properties and interaction capabilities(4). vimentin is one of these intermediate filaments (IFs)(6).

Vimentin, a type III intermediate filament (IF) protein, is traditionally recognized as a marker of mesenchymal cells. However, its expression extends beyond mesenchymal cells and has been documented in mature cardiac cells, including cardiomyocytes, where it persists into adulthood despite decreased levels during development, suggesting a crucial and persistent function in the mature heart(7-10). Far from being a mere structural element, vimentin is a versatile protein with multifaceted roles in cardiomyocytes. It provides critical structural support essential for contraction, acts as a signaling platform influencing cell growth and survival, regulates cardiac contractility, offers protection against damage, and helps maintain proper nuclear positioning(11).

Emerging evidence highlights the role of stromal cells, particularly telocytes, in cardiac remodeling and extracellular matrix (ECM) organization. Telocytes, a specialized population of interstitial cells, are implicated in mechanotransduction, ECM modulation, and intercellular signaling, partly through their vimentin-rich cytoskeleton(12). These cells interact closely with cardiomyocytes and fibroblasts, facilitating structural adaptations in response to physiological stimuli such as exercise training. For instance, endurance training has been shown to increase telocyte density, suggesting their potential involvement in exercise-induced cardiac hypertrophy and ECM remodeling(13, 14). Given vimentin's dual role as a structural and signaling molecule in both

cardiomyocytes and telocytes, its regulation may serve as a nexus for understanding exercise-mediated cardiac adaptations.

The literature examining the influence of exercise on vimentin levels is scarce. In a 2024 study, Godwin and colleagues examined the impact of resistance training and mechanical overload on vimentin levels within human and mouse skeletal muscle. Their findings revealed that skeletal muscle vimentin expression is sensitive to mechanical stress. Specifically, they observed an upregulation of vimentin after 10 weeks of resistance training in humans and a higher concentration of vimentin within the extracellular matrix (ECM) following 10 and 20 days of mechanical overload in mice(15). This suggests that vimentin is responsive to exercise-induced mechanical stimuli. However, the specific impact of exercise training on cardiac vimentin remains unexplored. Different exercise modalities impose distinct mechanical and metabolic loads on the heart(16). High-Intensity Interval Training (HIIT) subjects the heart to rapid and drastic changes in pressure and volume, resistance training primarily increases pressure load, and moderate-intensity continuous training (MICT) imposes a sustained volume load(17). These distinct hemodynamic patterns are likely transduced into differential cytoskeletal remodeling signals, potentially through mechanisms involving mechanotransduction pathways and oxidative stress(18, 19). We hypothesize that these distinct mechanical stresses will differentially regulate the expression of vimentin, a key cytoskeletal protein critical for myocardial structural integrity and signaling.

Therefore, this study aims to address this significant gap in knowledge by investigating and comparing the effects of these three distinct exercise training models—HIIT, resistance training, and MICT—on cardiac vimentin expression levels.

2. Methods and Materials

2.1. Animals

In the present experimental study, 32 healthy male Wistar rats (8 weeks old, average weight of 218.6±13.8 grams) were purchased from the Pasteur Institute of Iran. The animals were randomly divided into four equal groups (n=8): control, resistance training (RT), endurance training (ET), and high-intensity interval training (HIIT) groups. All animals were maintained under identical controlled laboratory conditions at a temperature of 22 ± 3°C, a 12-hour light-dark cycle, humidity of 40–60%, and free access to food and water, and were housed in polyethylene cages. To reduce stress and familiarize the animals with the new environment, the rats were kept for one week after transfer to the laboratory for acclimatization. All experimental procedures and interventions were conducted in accordance with international guidelines for the ethical care and use of laboratory animals (NIH Publication No. 85-23, revised 1996). The study received ethical approval from the Research Ethics Committee at the Sport Sciences Research

Institute of Iran (Approval ID: IR.SSRI.REC.1397.276).

2.2. Exercise training

Rats underwent a one-week adaptation period to acclimate to the exercise protocols. For resistance training, a vertical ladder (1 meter in height, 85-degree incline, with 2 cm spaced rungs) was utilized. Following the adaptation phase, during the first week of training, weights equivalent to 30% of the animals' body weight were attached to the distal part of their tails (1–2 cm below the fur line). The training load progressively increased to 200% of their body weight by the end of the eighth week. A successful repetition was defined as the rat climbing the entire ladder within approximately 8 seconds. The rats were positioned at the base of the ladder and encouraged to climb using mild stimuli (e.g., gentle taps on the tail or rungs). No unnatural stimuli, such as electric shocks, cold water, or air pressure, were employed. The training program consisted of 5 sessions per week over 8 weeks, with each session comprising 3 sets of 5 repetitions. Rest intervals included 2 minutes between sets and 1 minute between repetitions. Additionally, rats performed a 5-repetition set without weights at the beginning (1-minute rest between repetitions) and end (3-minute rest between repetitions) of each session for warm-up and cool-down purposes (20).

In the endurance and high-intensity interval training protocols, the rats' maximal oxygen consumption (VO_2max) was first assessed using an indirect but highly accurate protocol. In this protocol, the rats first warmed up at a speed of 5 meters per minute for 5 minutes. Then, the speed was increased to 10 meters per minute, and the rats began running. Subsequently, the treadmill speed was increased by 0.03 meters per second every two minutes until the rats reached maximum exhaustion and were unable to continue running. We confirm lactate measurements were integral to our VO_2max testing. At exhaustion, blood lactate reached 8–10 mmol/L in all rats (measured via Lactate Scout), verifying consistent maximal effort. This protocol aligns with rodent exercise physiology standards. The exercise intensity for each rat was calculated using the formula y= 162x - 1 (21). Subsequently, an 8-week exercise regimen (5 sessions per week) based on a percentage of VO_2max was implemented. Endurance training group Performed 5–10 minutes of warm-up at 50–60% VO_2max, followed by 50 minutes of continuous exercise at 65–70% VO_2max, and concluded with 5 minutes of cool-down at 50–60% VO_2max. ET duration was gradually increased: 20 min (Week 1), 30 min (Week 2), 40 min (Week 3), and 50 min (Weeks 4–8). (22). HIIT group Completed 60-minute treadmill sessions, including a 5–10 minute warm-up, 5 high-intensity intervals (8 minutes at 85–90% VO_2max) alternating with 2-minute recovery periods (50–60% VO_2max), and a 5-minute cool-down (22, 23). The weekly exercise intensity increased based on previous studies and the relationship between running speed and VO_2max,

with 0.02 meters per second added to the speed each week (21). The key parameters of these protocols are summarized in Table 1. Control group did not engage in any exercise during this period.

Table 1: Summary of Exercise Training Protocols

Parameter	Resistance Training (RT) Group	Endurance Training (ET) Group	High-Intensity Interval Training (HIIT) Group
Modality	Vertical Ladder Climbing	Treadmill Running	Treadmill Running
Duration	8 weeks	8 weeks	8 weeks
Frequency	5 sessions/week	5 sessions/week	5 sessions/week
Session Duration	45-50 min (incl. warm-up & cool-down)	60-65 min (Weeks 4-8; incl. warm-up & cool-down)	60 min (incl. warm-up & cool-down)
Intensity	Load: Progressive from 30% to 200% of body weight	Intensity: 65-70% of VO_2max (main phase)	High-Intensity Intervals: 85-90% of VO_2max Recovery Intervals: 50-60% of VO_2max
Volume & Pattern	Sets/Reps: 3 sets × 5 reps Rest: 2 min (between sets), 1 min (between reps) Progression: Load increased weekly	Pattern: Continuous running Progression: Duration increased from 20 min (Week 1) to 50 min (Weeks 4-8)	Pattern: 5 intervals of 8 min high-intensity, alternating with 2 min active recovery Progression: Speed increased by 0.02 m/s weekly
Warm-up/Cool-down	Warm-up: 5 reps (no load) Cool-down: 5 reps (no load)	Warm-up: 5-10 min at 50-60% VO_2max Cool-down: 5 min at 50-60% VO_2max	Warm-up: 5-10 min at 50-60% VO_2max Cool-down: 5 min at 50-60% VO_2max

2.3. Cardiac vimentin assessment

To investigate changes in vimentin expression in response to exercise training, immunofluorescence staining was employed. Following tissue fixation, dehydration (with ethanol), clearing, and cardiac tissue embedding, 5-µm-thick sections were prepared using a microtome. The samples were initially washed with phosphate-buffered saline (PBS) in three steps (5 minutes each). For epitope retrieval, citrate buffer (pH=6) with heat treatment in a water bath (95–100°C for 20 minutes) was used instead of hydrochloric acid. The samples were then rinsed with PBS and treated with borate buffer (5 minutes) for neutralization. Membrane permeabilization was performed using 0.3% Triton X-100 (in PBS) for 30 minutes. After PBS washing, non-specific blocking was conducted with 10% goat serum (in PBS) for 30 minutes. The primary anti-vimentin antibody diluted 1:100 in PBS was applied to the samples. The samples were incubated overnight at 4°C in a humidified chamber (using a moisture-retaining container) to prevent tissue drying. The next day, the samples were washed with PBS in three steps (5 minutes each). A secondary antibody conjugated with Alexa Fluor 488 fluorochrome (diluted 1:150 in PBS) was added, and the samples were incubated at 37°C for 1 hour in darkness. Following a final PBS wash, nuclear staining was performed using DAPI (1 µg/mL for 5 minutes). The samples were coverslipped with an anti-fade mounting medium (90% glycerol + DABCO) and examined under

an Olympus fluorescence microscope at 400× magnification.

2.4. Statistic

Following data collection, statistical analysis was performed using SPSS software (version 26). Results are expressed as mean ± SEM, and a significance level of $P \leq 0.05$ was applied. The normality of data distribution was first confirmed using the Shapiro-Wilk test. We used one-way analysis of variance (ANOVA) To compare mean values across the four study groups. In cases of significant differences, Tukey's post hoc test was utilized to identify specific group disparities.

3. Results

There was a significant difference in cardiac vimentin levels among the experimental groups (P=0.0001, $\eta^2 = .94$). To determine the source of this difference, Tukey's post hoc test was employed. Resistance training (RT), endurance training (ET), and high-intensity interval training (HIIT) significantly increased cardiac vimentin levels compared to the control group. This increase was significantly greater in the HIIT group compared to the ET (P=0.001) and RT groups (P=0.0001), indicating the influence of exercise intensity on the expression of this protein (Figure 1 and Figure 2).

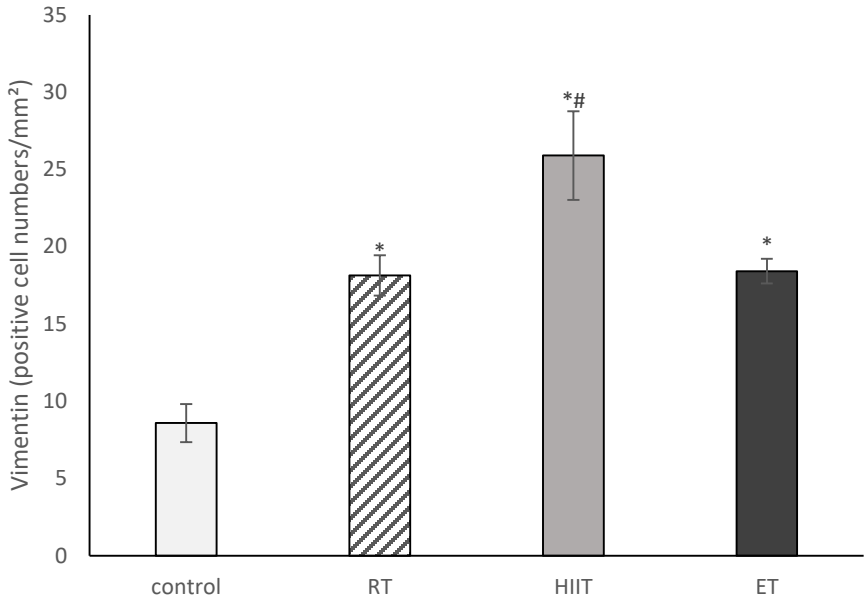

Figure 1. Vimentin levels were quantified by measuring fluorescence intensity in immunofluorescence images of cardiac tissue sections (n=8 animals per group). Data are presented as mean ± SEM. *: significantly different from the control group. #: significantly different from the RT and ET groups. RT: resistance training group. HIIT: high intensity interval training group. ET: endurance training group.

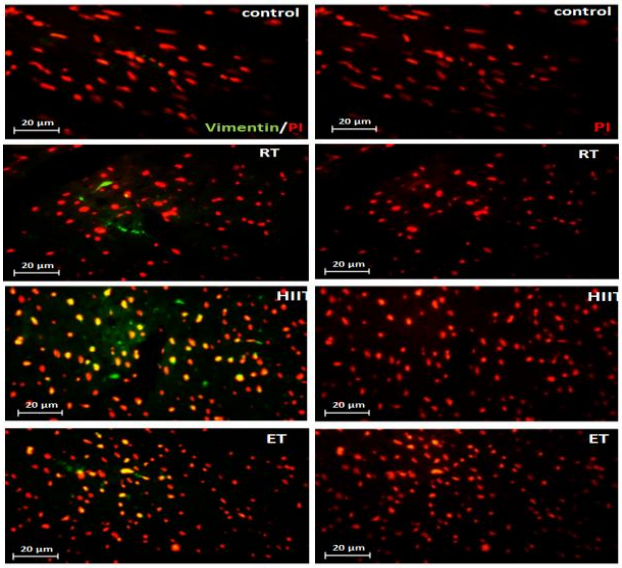

Figure 2. Immunofluorescence analysis of cardiac vimentin expression (green) following eight weeks of endurance training (ET), resistance training (RT), and high-intensity interval training (HIIT). Representative images showing the vimentin signal are displayed. Scale bar: 20 µm.

4. Discussion

The findings of this study demonstrate that resistance training (RT), endurance training (ET), and high-intensity interval training (HIIT) significantly elevate cardiac vimentin levels in male Wistar rats, with HIIT emerging as the most potent stimulus for upregulating this protein. These results provide novel insights into exercise-induced cardiac adaptations and underscore the importance of exercise modality in modulating cytoskeletal remodeling.

Our results align with the limited existing exercise literature. For instance, Godwin et al. (2024) reported elevated vimentin levels in skeletal muscle following 10 weeks of resistance training, underscoring potential tissue-specific adaptations(15). The pronounced increase in vimentin following HIIT is likely attributable to its unique capacity to impose greater mechanical and metabolic stress on the heart(24). Specifically, The cyclical nature of HIIT—alternating high-intensity bouts (85–90% VO_2max) with recovery phases—generates repeated hemodynamic challenges, which may stimulate stromal cells such as telocytes ($CD34^+$/$vimentin^+$ cells)(13). Telocytes are known to regulate extracellular matrix (ECM) organization and may drive vimentin secretion to reinforce myocardial structural integrity, a mechanism potentially conserved across exercise modalities (14).

Our findings of exercise-induced upregulation of cardiac vimentin appear to contrast with studies conducted in cancerous tissues. For instance, studies by Gholamian et al. demonstrated that aerobic interval training significantly reduced the expression of vimentin in breast tumor tissue in mice, an effect associated with

inhibited tumor progression and metastasis(25, 26). This apparent discrepancy highlights the critical context-dependent role of vimentin. In cancer, vimentin is a key marker of the epithelial-mesenchymal transition (EMT), a process associated with metastasis and aggressiveness. Therefore, its downregulation by exercise is considered a beneficial outcome(25). Conversely, in the healthy myocardium, vimentin is a fundamental structural component of the cytoskeleton in fibroblasts and other cells, crucial for maintaining mechanical integrity and facilitating adaptive responses. The increase we observed likely represents a positive adaptive mechanism to exercise-induced mechanical stress, aimed at reinforcing cardiac tissue structure. This dual nature of vimentin underscores the importance of the tissue environment (pathological vs. physiological) in interpreting its regulation(7).

However, given vimentin's association with fibrosis in disease states, we considered whether its increase could signal maladaptive remodeling. We deem this unlikely because the used exercise protocols are cardioprotective and not associated with pathological fibrosis in healthy models. They typically improve function and promote physiological hypertrophy, contrasting with fibrotic impairment. Nevertheless, future studies directly assessing fibrotic markers (e.g., collagen deposition, TGF-β) alongside vimentin are essential to conclusively affirm the adaptive nature of this response.

A key limitation is the use of semi-quantitative immunofluorescence, potentially overlooking subtle expression changes. Our vimentin-centric approach also precluded assessment of other ECM proteins. Most critically, the lack of direct fibrotic marker and cardiac function measurement limits definitive conclusions on the adaptiveness of vimentin increase. Future work must employ quantitative techniques (Western blot, qPCR), incorporate integrative ECM analyses, and assess cardiac function to link structural changes to outcomes. Isolating specific cell types (e.g., telocytes, fibroblasts) could further clarify their contributions. Longitudinal and sex-specific studies are also warranted.

In conclusion, the findings suggest that exercise training, particularly HIIT, may enhance cardiac structural adaptations by increasing cardiac vimentin levels. The differences observed between exercise groups indicate that exercise intensity likely plays a pivotal role in cytoskeletal regulation. However**,** the current scientific debate on exercise-mediated vimentin regulation is limited by the near absence of cardiac-specific studies, underscoring the exploratory nature of our work. Therefore**,** future studies are needed to elucidate the precise mechanisms and assess the generalizability of these results to humans.

5. Conclusion

The findings indicate that exercise training, particularly high-intensity interval training (HIIT), increases cardiac vimentin levels in rats. This increase may represent a structural

adaptation in response to exercise-induced mechanical stress. However, given the dual role of vimentin in both physiological and pathological processes, these results should be interpreted with caution. To determine the exact nature of this response, future studies that simultaneously assess changes in vimentin alongside markers of cardiac function and fibrosis are essential.

Conflict of interest

The authors declared no conflicts of interest.

Authors' contributions

All authors contributed to the original idea, study design.

Ethical considerations

The author has completely considered ethical issues. The study received ethical approval from the Research Ethics Committee at the Sport Sciences Research Institute of Iran (Approval ID: IR.SSRI.REC.1397.276).

Data availability

The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

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