Nature and Science of Sleep

Elevate Series

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ORIGINAL RESEARCH

Effects of Aerobic Exercise on Myocardial Injury in Sleep Deprived Mice

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Purpose: To investigate the effect of aerobic exercise on myocardial injury in sleep deprived mice, and explore the possible causative role.

Methods: Forty male C57BL/6J mice were randomly assigned to five groups (n=8/group): control (Ctrl), sleep deprivation for 7 or 28 days (SD7, SD28), and sleep deprivation with daily 7% weight-bearing exhaustion swimming for 7 or 28 days (SD+ES7, SD+ES28). Mental behavior was observed, cardiac markers were analyzed through blood biochemistry, and myocardial structures were examined using H&E staining.

Results: Compared to the Ctrl group, mice in each experimental group showed reduced body weight ($p < 0.001$). The levels of alpha-hydroxybutyrate dehydrogenase were significantly higher in the SD7 group ($p < 0.01$) and lower in the SD+ES7 group. Regarding creatine kinase expression, it was elevated in the SD7, SD28 and SD+ES28 groups ($p < 0.05$), but lower in the SD+ES7. Creatine kinase-MB was notably higher in the SD7 group ($p < 0.01$), and significantly reduced in the SD+ES7, SD28, and SD+ES28 groups ($p < 0.01$). High-sensitivity troponin T level was significantly higher only in the SD7 group ($p < 0.01$). Histological examination by H&E staining revealed varying degrees of cardiomyocyte swelling, morphological changes, widened intercellular spaces, disordered arrangement of myocardial fibers and infiltration of inflammatory cells in all experimental groups. Importantly, compared to the SD group at the corresponding time point, the SD+ES group showed attenuated pathological changes, with reduced myocardial edema. However, the SD+ES28 group still exhibited some inflammatory cell infiltration and perinuclear blank areas.

Conclusion: Sleep deprivation can cause myocardial ischemic injury and structural changes in cardiomyocytes, which is most prominent biochemically in the initial week. Daily exhaustion swimming, as an aerobic exercise, may have a short-term protective effect on the myocardium. With prolonged sleep deprivation, the compensatory mechanism of aerobic exercise may be exhausted.

Keywords: sleep deprivation, exhaustion swimming, myocardial injury

Introduction

Sleep plays a crucial role in maintaining physical and mental health that accounts for about 1/3 of human life. Adults typically need 7–8 hours of sleep each night, while teenagers need 8–10 hours.[1,2] However, the demands of contemporary life - such as occupational obligations, academic responsibilities, and social activities - tend to create an environment that encourages long periods of wakefulness. As a result, numerous individuals experience sleep deprivation (SD),[3,4] either actively or passively, and often do not realize the consequences.

There was research indicating a link between short sleep duration and mortality, with a 12% to 35% increased risk of death when sleeping less than 7 hours per night.[5] Several studies have shown that sleeping less than 6 hours significantly increases the risk of coronary artery disease, myocardial infarction, non-fatal cardiovascular events, and cardiovascular death.[6–8] A study has shown that 72h of REM sleep deprivation increased the latency times of premature ventricular contraction (PVC), ventricular tachycardia (VT), and also the PVC number, but not increase the number, duration, and severity of lethal VT and ventricular fibrillation (VF).[9] Another study showed that rats deprived of REM sleep for 4 days had significantly increased NOx level in heart, coronary flow CK-MB and LDH and infarct size after myocardial

Received: 12 August 2025
Accepted: 21 November 2025
Published: 23 December 2025

ischemia-reperfusion.[10] The impact and pathological mechanisms of SD on cardiac function need to be further explored, especially in terms of long-term effects.

As we all know, both aerobic and resistance exercise training, even at less than the recommended targets in the current exercise guidelines, are widely recognized as essential components of a healthy lifestyle and an effective non-pharmacological preventive strategy for CVD.[11] Some studies have shown that exercise may be an effective measure for treating short-term sleep deprivation for mitigating the negative effects of sleep loss on metabolic markers.[12] There was also a study indicating that aerobic exercise can attenuate, but does not fully reverse, the augmented 24-h ambulatory blood pressure (BP) response caused by acute partial sleep deprivation (PSD).[13] A recent narrative review concluded that sleep deprivation can lead to autonomic imbalance, elevated blood pressure, and increased inflammatory response, and moderate and severe activity may exacerbate these symptoms and increase cardiovascular burden.[14] Giampá conducted a 96 hour sleep deprivation experiment on rats based on an 8-week last resistance training session, which observed that sleep deprivation reduced serum testosterone and insulin-like growth factor-1 (IGF-1), and increased corticosterone and angiotensin II, leading to cardiac dysfunction, while prophylactic resistance training reduced this degree.[15]

However, few studies have elucidated whether aerobic exercise can prevent the negative effects of SD on cardiac function from the perspective of myocardial ischemia. Previous studies have mainly focused on the relationship between aerobic exercise and myocardial ischemia after coronary artery disease, proving that high-intensity interval training was superior to moderate-intensity continuous training in effective therapy for improving coronary artery disease, but has a weak effect for heart failure.[16,17] Further animal and cell experiments have demonstrated that this improvement may work through multiple pathways. For example, scholar Zhang has demonstrated that Aerobic exercise training attenuates myocardial ischemia-reperfusion injury by reducing the level of METTL3-related m6A RNA methylation in cardiomyocytes and activating the Nrf2/HO-1 antioxidant signaling pathway,[18] and scholar Liu has proved that exercise alleviates programmed necrosis in myocardial ischemia-reperfusion injury through adipose tissue-derived exosomal miR-17-3p targeting CAMKII.[19]

Therefore, this study aims to determine the effects of SD on short-term and long-term myocardial injury in mice, and further evaluated whether aerobic exercise can alleviate the negative effects of SD on myocardial injury.

Methods

Animals

A total of 40 male C57BL/6J mice (8 weeks of age, 21.70±0.64g body weight) were purchased from Hunan SJA Laboratory Animal Co., Ltd. According to the literature review, the animals were housed in groups of eight under standard conditions (12-hour light/dark cycle with lights on at 8:30 AM, temperature of 22.0–24.0°C, and humidity at 55 ±5%) and allowed free access to food and water. This study adhered to The ARRIVE guidelines and relevant regulations. All animal procedures were approved by the Animal Protection and Use Committee of the Second Xiangya Hospital, Central South University (Approval No. 2021556).

Experimental Procedures

After one week of adaptive feeding, the mice were randomly divided into five groups using a computer-based random sequence generator: control group (Ctrl), SD for 7 days group (SD7), SD for 28 days group (SD28), SD+ weight-bearing exhaustion swimming for 7 days group (SD+ES7), and SD+ weight-bearing exhaustion swimming for 28 days group (SD +ES 28), with 8 mice in each group (n = 8 mice per group, total n = 40 mice). Based on guidelines and literature related to sleep deprivation, it was recommended that a minimum of five independent animals per group for histopathology studies can provide adequate power.[20–22] The sample size of this study was eight per group, which met the general requirements for animal experiments. For each mouse, two researchers were involved as follows: a first researcher performed the sleep deprivation and weight-bearing exhaustion swimming interventions according to the experimental groupings. A second researcher was responsible for the final collection of samples and sending them for testing. The Ctrl group mice were housed in standard conditions with unrestricted access to sleep, as shown in Figure 1.

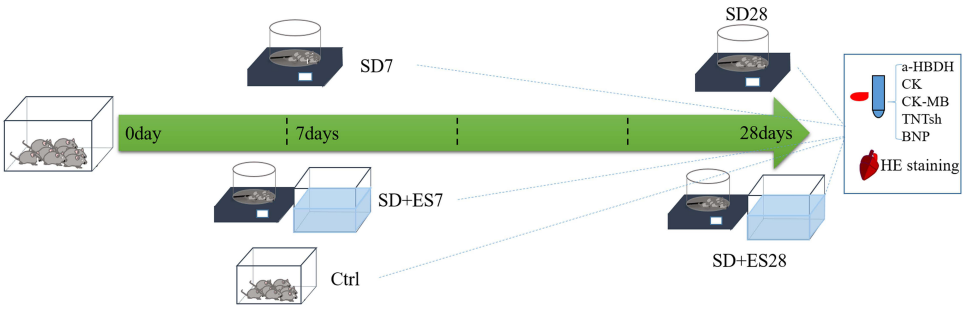

Figure 1 Schematic Representation of the Experimental Design.
Abbreviations: Ctrl, control group; SD, sleep deprivation; ES, exhaustion swimming.

Sleep Deprivation

All mice in the experimental groups underwent SD using a newly developed apparatus, which operates by rotating interference rods that wake the mice upon contact if they fall asleep. The sleep deprivation apparatus was set to 22 hours per day, with a rotation speed of 6.0 RPM, 10-second intervals, and alternating 30-second deprivation phases. Deprivation was paused for 2 hours daily from 16:00 to 18:00, resuming at 18:01. Mice had free access to movement, food, and water, and the environmental conditions were maintained as specified earlier.

Weight-Bearing Exhaustion Swimming

Mice in the SD+ES7 and SD+ES28 groups underwent daily exhaustive swimming training with a lead weight (7% of body weight) tied to their tails. The training was conducted in a rectangular plastic pool (79 cm × 56.5 cm × 48 cm) with water at 30±2°C and a depth of 30±1 cm, preventing the mice from touching the bottom. The time to exhaustion was recorded, starting when the mouse entered the water and stopping when its nose stayed submerged for 10 seconds, which defined exhaustion. This paradigm provided a validated, high-intensity aerobic stressor to test our hypothesis that exercise adaptations can mitigate sleep deprivation-induced myocardial pathology.

Sample Collection

The mice were monitored for changes in fur color, activity, mental state, food and water intake, and urination/defecation. Body weight was measured every 4 and 7 days at 8 a.m. using a standardized weighing box and electronic scale. At the end of the experiment, deep anesthesia was induced with pentobarbital sodium (50 mg/kg). Once the loss of corneal reflex was achieved, the mice were subsequently euthanized via terminal blood collection by orbital puncture. Then, the heart was excised, weighed, fixed, and processed for H&E staining. The blood was centrifuged at 3500 rpm for 10 minutes to obtain serum, and then sent for biochemical analysis and examination using the Roche Cobas 8000 fully automatic biochemical analyzer, which was carried out at the clinical biochemical testing center of the hospital. The serum alpha-hydroxybutyrate dehydrogenase (a-HBDH), Creatine kinase (CK), and creatine kinase-MB (CK-MB) were respectively detected using a-HBDH Assay Kit (a-keto butyrate substrate method), CK Assay Kit (creatine Phosphate Substrate Method), CK-MB isoenzyme assay kit (immunosuppressive method) by using Cobas c 702. The serum high-sensitivity troponin T (TNTsh) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were respectively detected elecsys Troponin Ths and NT-proBNP (electrochemiluminescence Immunoassay) by using Cobas e 801.

Observational Indicators

Observational indicators included: ①The heart weight index: Heart weight index = heart weight (g) / body weight (g). ②Exhaustive swimming time. ③Serum blood indices included a-HBDH, CK, CK-MB, TNTsh, and NT-proBNP ④Observe changes in myocardial tissue structure after H&E staining.

https://doi.org/10.2147/NSS.S559465

Statistical Analysis

All data were analyzed and visualized using SPSS 26.0 and Origin 2017 software. The results are presented as mean ± standard deviation. Comparisons between groups were performed using one-way ANOVA, followed by LSD-t for post-hoc analysis. Repeated measures ANOVA was applied to assess the changes in exhaustion swimming times before and after the experiment within each group. $p < 0.05$ was considered statistically significant.

Result

Routine Health Assessment of Mice in Each Group

Compared to the Ctrl group, mice in the SD7 and SD+ES7 groups showed poor mental state, dull and lackluster fur, reduced activity, with normal food and water intake. Some SD+ES7 mice appeared extremely lethargic. In the SD28 and SD+ES28 groups, mice exhibited mental fatigue, disheveled fur, and significantly reduced activity, while maintaining normal food and water intake. As the experiment progressed, both the SD28 and SD+ES28 groups developed abnormal behaviors, including feces consumption, biting, and irritability. Unfortunately, on the final day of the experiment, one mouse from each of the SD+ES7 and SD+ES28 groups passed away.

Variations in Body Weight, Heart Weight, and the Heart-to-Body Weight Index

As shown in Table 1 and Figure 2, compared with before the experiment (Figure 2A), the body weights of mice in the SD7, SD+ES7, SD28, and SD+ES28 groups were significantly reduced at the end of the experiment (Figure 2C), with final body weights lower than the Ctrl group (Table 1, $p < 0.001$). Notably, the SD+ES28 group exhibited the most substantial weight loss, which was significantly greater than that of the SD7 group (Figure 2B, $p < 0.001$), while no significant differences were found when compared to the SD+ES7 and SD28 groups ($p > 0.05$). Furthermore, no significant differences were observed in heart weight or heart-to-body weight ratio across all five groups ($p > 0.05$).

Effect of SD on the Physical Endurance of Mice

To assess the effect of SD on exercise endurance in mice, we compared the daily exhaustion swimming duration of the SD+ES7 group and the weekly average exhaustion swimming duration of the SD+ES28 group. As shown in Figure 3A, the sphericity test for the SD+ES7 group yielded $w < 0.001$, $p = 0.018$, indicating a violation of the sphericity assumption, with degrees of freedom corrected using Greenhouse-Geisser ε, and the overall comparison revealed no significant difference in daily exhaustion swimming duration ($F = 9.812$, $p = 0.240$). In the SD+ES28 group, the weekly average exhaustion swimming time increased slowly from 450.75s in week1 to 537.63s in week3, and then sharply decreased to 484.63s in the fourth week, though these differences were not statistically significant (Figure 3B, $w = 0.464$, $p = 0.500$, $F = 0.869$, $p = 0.438$), indicating that the mice rapidly exhausted their physical strength after the third week.

Effects of SD on the Expression Levels of Relevant Serum Markers of Cardiac Function

a-HBDH Expression in Five Groups

The a-HBDH expression levels in the five groups of mice were statistically significant ($p < 0.001$). Specifically, a-HBDH was significantly higher in the SD7 group compared to the Ctrl group ($p < 0.01$), and significantly lower in the SD+ES7 group ($p < 0.01$). No significant difference was observed between the SD28 and SD+ES28 groups ($p > 0.05$). Additionally, a-HBDH levels in the SD7 group were higher than in the SD+ES7, SD28, and SD+ES28 groups ($p <$

Table 1 Comparison of Body Weight, Heart Weight, and Heart-to-Body Weight Ratio

	Ctrl (n=8)	SD7 (n=8)	SD+ES7 (n=7)	SD28 (n=8)	SD+ES28 (n=7)	P Value
Body Weight (g)	24.87±1.27	22.91±1.32	22.23±0.92	23.27±0.71	24.68±0.94	<0.001
Heart weight (g)	0.15±0.02	0.11±0.03	0.14±0.04	0.14±0.02	0.15±0.01	0.218
HTB weight ratio (%)	0.61±0.10	0.51±0.16	0.63±0.17	0.59±0.09	0.61±0.04	0.599

Abbreviations: Ctrl, control group; SD, sleep deprivation; ES, exhaustion swimming; HTB, heart-to-body.

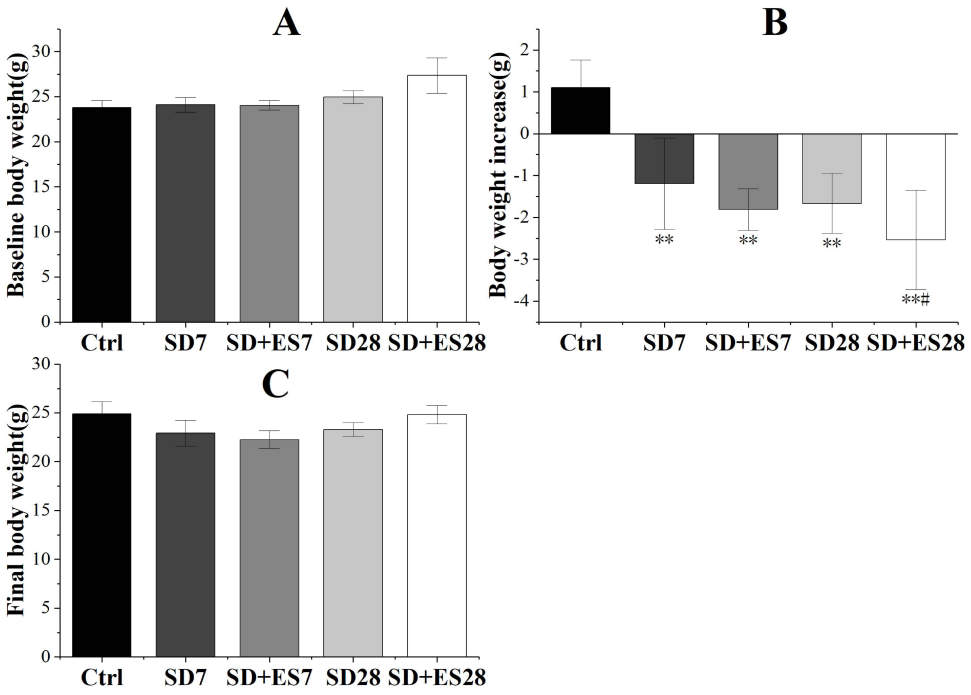

Figure 2 Results of Weight Changes in Each Group of Mice.
Notes: Data are presented as the mean ± standard error (M ± SE) (n = 8 mice per group). (**A**) Baseline body weight comparison across groups; (**B**) Comparison of body weight increase across groups; (**C**) Comparison of final body weight across groups. Compared to Ctrl group **p < 0.001; Compared to SD7 group, #p < 0.001.
Abbreviations: Ctrl, control group; SD, sleep deprivation; ES, exhaustion swimming.

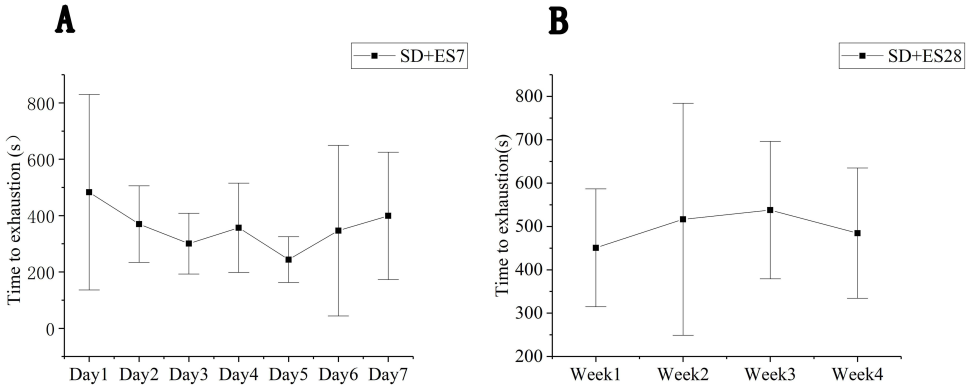

Figure 3 Exhaustion Swimming Duration.
Notes: Data are presented as the mean ± standard error (M ± SE) (n = 8 mice per group). (**A**) The daily exhaustion swimming duration of the SD+ES7 group; (**B**)The weekly average exhaustion swimming duration of the SD+ES28 group.
Abbreviations: Ctrl, control group; SD, sleep deprivation; ES, exhaustion swimming.

0.01), while the SD+ES7 group had lower levels than the SD28 ($p < 0.05$) and SD+ES28 ($p < 0.01$) groups, as shown in Table 2.

CK Expression in Five Groups

The CK expression in the five mouse groups showed statistical significance ($p < 0.001$). Compared to the Ctrl group, CK levels were significantly higher in the SD7 ($p < 0.01$), SD28 ($p < 0.05$), and SD+ES28 ($p < 0.05$) groups, while no significant difference was found in the SD+ES7 group ($p > 0.05$). Moreover, CK levels in the SD7 group were notably higher than those in the SD+ES7 ($p < 0.01$), SD28 ($p < 0.05$), and SD+ES28 ($p < 0.05$) groups. The SD+ES7 group had lower CK levels than the SD28 ($p < 0.05$) and SD+ES28 ($p < 0.05$) groups, as shown in Table 2.

https://doi.org/10.2147/NSS.S559465

Table 2 a-HBDH, CK, CK-MB and TNTsh Expression in Five Groups

	Ctrl	SD7	SD+ES7	SD28	SD+ES28	P Value
a-HBDH (u/L)	130.13±14.35	188.90±32.27**	94.76±19.20**##	119.85±22.80##	128.59±17.19##	<0.001
CK (u/L)	1029.46±348.17	2266.50±762.70**	950.57±298.27##	1623.13±409.16*#†	1630.29±590.01*#†	<0.001
CK-MB (u/L)	360.18±45.70	453.01±65.76**	195.44±13.33**##	259.35±54.53**##†	250.04±56.95**##	<0.001
TNTsh (ng/L)	24.69±9.31	47.04±27.33**	21.40±6.53##	27.81±6.56#	30.01±6.85##	<0.001

Notes: Compared to the Ctrl group, *P<0.05,**P<0.01; compared to the SD7 group, # P<0.05, ## P<0.01; compared to the SD+ES7 group, †P<0.05.
Abbreviations: a-HBDH, alpha-hydroxybutyrate dehydrogenase; CK, Creatine kinase; CK-MB, creatine kinase-MB; TNTsh, high-sensitivity troponin T; Ctrl, control group; SD, sleep deprivation; ES, exhaustion swimming.

CK-MB Expression in Five Groups

The CK-MB levels in the five mouse groups were significantly different ($p < 0.001$). Compared to the Ctrl group, CK-MB was notably higher in the SD7 group ($p < 0.01$), and significantly lower in the SD+ES7, SD28, and SD+ES28 groups ($p < 0.01$). Pairwise comparisons indicated that CK-MB in the SD7 group was higher than in the SD+ES7, SD28, and SD +ES28 groups ($p < 0.05$). Moreover, CK-MB in the SD+ES7 group was lower than in the SD28 ($p < 0.01$) and SD+ES28 ($p < 0.05$) groups, as shown in Table 2.

TNTsh Expression in Five Groups

The TNTsh levels in the five mouse groups differed significantly ($p < 0.001$). Compared to the Ctrl group, TNTsh was significantly higher in the SD7 group ($p < 0.01$), with no significant differences observed in the SD+ES7, SD28, and SD +ES28 groups ($p > 0.05$). Pairwise comparisons showed that TNTsh in the SD7 group was higher than in the SD+ES7 ($p < 0.01$), SD28 ($p < 0.05$), and SD+ES28 ($p < 0.05$) groups, as shown in Table 2.

NT-proBNP Expression in Five Groups

The NT-proBNP levels were below 5 ng/L in all mice.

Impact of SD on Mouse Myocardial Tissue Structure

Compared with the Ctrl group, the myocyte gap was enlarged, cell irregular arrangement, disordered arrangement of longitudinal myocardial fibers, and infiltration of a small amount of inflammatory cells in the SD7 group. In the SD28 group, significantly the cellular morphology and structure had abnormalities, larger gaps between myocardial cells, disordered and loose some of the myofibrils, and increased inflammatory infiltration. Compared with the SD7 group, the edema of myocardial cells has decreased, but there is still infiltration of inflammatory cells in the SD+ES7 group. In the SD28 group, myocardial cells and fibers were arranged more tightly, with blank areas around some cell nuclei and a small amount of inflammatory cell infiltration. The H&E staining results were shown in Figure 4.

Discussion

SD Can Cause Weight Loss in Mice

Body weight is one of the most commonly observed indicators in SD experiments. Studies have shown that SD is an essential risk factor for weight gain and obesity in humans, which is associated with alterations in dietary habits, metabolic rate and hormones that regulate metabolism.[23–26] In contrast, this study found that SD can significantly reduce body weight in mice. There may be complex reasons that SD in humans often triggers emotional eating, particularly increasing cravings for high-sugar and high-fat foods, whereas for mice there was no difference in the food offered before and after SD in a strictly experimental setting. Similar to the findings of this study, some studies found SD can lead to malnutrition and weight loss,[10,27] which could be linked to the fact that SD is a strong stressor, which leads to cause homeostatic imbalance, metabolic abnormalities, and increased energy expenditure in the body.

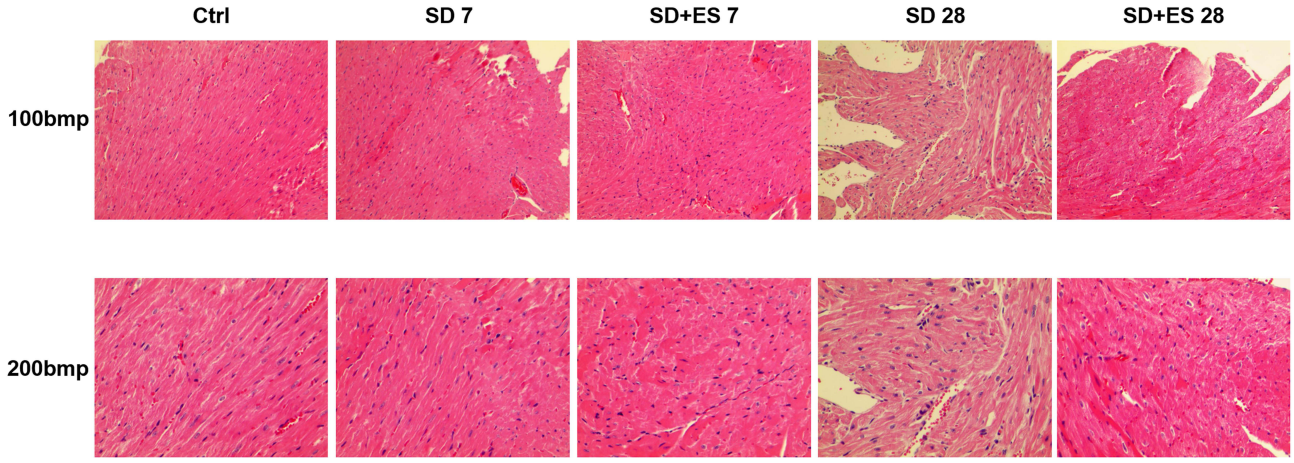

Figure 4 H&E Staining of Myocardial Structure in 5 Group of Mice.
Abbreviations: Ctrl, control group; SD, sleep deprivation; ES, exhaustion swimming.

SD Alters Exercise Endurance and Fatigue in Mice

Fatigue is primarily characterized by a decrease in exercise endurance, and time to exhaustion is a commonly used indicator of exercise endurance. A previous study showed that the sleep restriction group had significantly less time in exhaustion swimming versus the control group.[28] It suggests that SD caused the mice to have lower exercise endurance and made them enter a state of fatigue. In this study, it was found that swimming exercise can prolong the fatigue time of SD mice in the short term, but it rapidly decreases in the fourth week, leading to physical exhaustion. Swimming training, as an aerobic exercise, may enhance body function in the short term, but its long-term effects on sleep deprivation fatigue may be reduced. It is recommended to set up longer research periods and increase independent swimming control groups in the future. A Study results showed that c-Fos gene expression was relatively reduced in hippocampal neuronal activation in adult rats after endurance exercise to exhaustion, which may be a protective effect of stress hormone suppression.[29] In addition, the factors affecting swimming endurance in mice potentially include weight bearing, water temperature, and strain, and it is possible that locomotor ability and voluntary activity may be influenced by genetic factors under equal conditions.[30]

Effects of SD on Expression of Serologic Indices of Cardiac Function in Mice

Analysis of the Results of Serological Indexes in SD Group Mice

Heart is the motor of the circulatory system and is one of the most active organs. When myocardial ischemia necrosis and cell membrane permeability increase, cellular enzymes in the myocardium are released into the blood. In this experiment, mice in the SD7 group showed a significant increase in a-HBDH, CK, CK-MB, and TNTsh compared to the Ctrl group. In the SD28 group, CK levels were significantly higher, while CK-MB levels were significantly lower, with no significant differences observed in the other indices relative to the Ctrl group. Similar to the findings of this study, Jeddi S et al induced rapid eye movement (REM) sleep deprivation in rats using the flowerpot method for 96 hours, and myocardial tissues after ischemia-reperfusion in isolated hearts showed that increased expression of inducible nitric oxide synthase (iNOS), increased apoptosis, and myocardial CK-MB and LDH were all significantly higher than those in the control group, and myocardial infarction area increased.[31]

However, chronic SD may have complex biological consequences. It has been shown that SD can affect several biological pathways, such as neural autonomic control, oxidative stress, inflammatory responses, and endothelial function, all of which are pathophysiological mechanisms that are linked between SD and increased risk of cardiovascular disease.[32] Other studies have pointed out that long-term SD may cause the body to enter a state of chronic stress, in which, if inferior stressors persist in the organism, they activate the neuroendocrine system, as well as the release of hormones such as adrenaline and cortisol.[33] In this condition some biological parameters in the body may be altered, including the release of cardiac enzymes. Furthermore, such results may be related to the window period for the release

of cardiac enzymes into the bloodstream. In general, the window period for CK is hours to days after myocardial infarction. CK-MB is one of the isoforms of the creatine kinase isoform and has the highest specificity of all the isoforms. Following myocardial infarction, CK-MB concentrations usually peak within 4 to 6 hours and then gradually decline, returning to normal levels within 24 to 72 hours. Furthermore, it could not be ruled out that the increase in CK may be due to pressure damage caused by SD to skeletal muscles. In conjunction with the H&E staining results, it suggests that sleep deprivation can lead to myocardial injury ischemia or infarction, thus inducing sudden death.

Analysis of the Results of Serological Indexes in SD+ES Group Mice

In this experiment, the results showed that a-HBDH, CK, CK-MB, and TNTsh were significantly reduced in the SD+ES7 group of mice compared with the Ctrl and SD7 groups, which may indicate that moderate weight-bearing forceful swimming for a short period of time can relatively alleviate and mitigate myocardial injury caused by sleep deprivation. Unlike other studies that required mice to perform two hours of exhaustion swimming daily,[34] the present study only required mice to perform one exhaustion swim daily and did not limit the duration of swimming. For mice, this might be relatively appropriate weight training and aerobic training. Previous studies have demonstrated the role of moderate aerobic exercise in promoting faster blood flow, increasing cardiac loading capacity and improving myocardial blood supply.[35] Moreover, Rocchi et al found aerobic exercise to be a potent inducer of autophagy, a lysosomal degradation pathway necessary for the stability, function, and differentiation of the intracellular environment, in several organs in mice, as discovered in recent years.[36] Feng et al performed different kinds of exercise on mice revealed that resistance exercise attenuated prefrontal lobe injury and dysfunction in mice with myocardial infarction through activation of the SESN 2/AMPK/PGC-1α signaling pathway, inhibition of oxidative stress, and inhibition of inflammatory responses.[37] Consistent with other studies, the results of the present study support that moderate swimming has a protective effect on the myocardium, but the pathomechanism needs to be further investigated.

Other studies have proved that the body adapts to the higher aerobic demand and perfusion level brought about by aerobic exercise, and the arteries, small arteries and capillaries are adjusted structurally and quantitatively, thus enhancing the heart's loading capacity.[35] However, compared with the Ctrl group and the SD+ES7 group, a-HBDH and CK levels were significantly higher in mice in the SD+ES28 group, and CK-MB significantly lower. Even aerobic exercise cannot completely offset the damage caused by long-term SD, and H&E staining still shows myocardial injury. Compared with the SD28 group, there was no significant difference in the myocardial enzyme results of the SD+ES28 group mice, and showing less myofibrillar rupture and inflammatory cell infiltration, but blank areas appeared around the nucleus in the myocardial tissue. This may indicate that aerobic exercise can partially alleviate myocardial damage caused by long-term sleep deprivation, but long-term sleep deprivation leads to irreversible cell apoptosis and necrosis. In previous experimental studies, long-term aerobic exercise (3-week or 4-week swimming training) has been shown to alleviate myocardial ischemia-reperfusion injury by uptake of extracellular vesicles[19] or reduction of methylation levels[18] in related myocardial cells. However, further research is needed to investigate the mechanism of long-term sleep deprivation in this study. When there is obvious myocardial damage in the body, the additional load (exhaustive swimming) increases the risk of sudden death. On the last day of this experiment, two mice in the exhausted swimming group had their noses submerged in water for 10 seconds before being retrieved and dying. From the results, it would appear to be the result of chronic SD. In conclusion, the present study concluded that moderate weight-bearing exhaustion swimming has multiple benefits for cardiac function, which enhances the strength and endurance of the myocardium and improves the pumping efficiency of the heart, which in turn may partially resist the impairment of cardiac function by sleep deprivation.

There are also some limitations in our study. The NT-proBNP was less than 5 ng/L in all mice, which may be due to the lack of corin in the mice used in this experiment. It is known that corin can convert B-type natriuretic peptide (BNP) prohormone into BNP and its amino-terminal fragment (NT-proBNP).[38] Future studies should adopt a more accurate and effective method to detect it. The experimental design did not include a only fatigue swimming group, making it impossible to compare and analyze the net protective effect of exercise, which was also a limitation, although we focused on whether aerobic exercise can alleviate the damage caused by sleep deprivation. Particularly, this study was a preliminary research, and in the future, more rigorous experimental design, data presentation, and deeper cellular and molecular analysis will be needed for verification. In addition, this study could not directly determine whether sleep

deprivation could cause myocardial infarction, and further angiography and other methods are needed to determine this in subsequent studies.

Conclusion

In conclusion, this study established an animal model of SD+ES by using a novel SD apparatus to sleep deprive mice for 7 and 28 days, and then to intervene with once-daily weight-bearing forceful swimming. The results of the study showed that SD causes different degrees of elevation of serological indices of cardiac function (a-HBDH, CK, CK-MB, TNTsh), and structural changes in cardiomyocytes, and force-exhaustion swimming exercise may be able to reduce short-term myocardial injury caused by SD. With prolonged sleep deprivation, the compensatory mechanism of aerobic exercise may be exhausted. In the future, it is necessary to study the mechanisms between them by increasing the exercise control group and prolonging the intervention time.

Data Sharing Statement

The study data are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

All animal procedures were approved by the Animal Protection and Use Committee of the Second Xiangya Hospital, Central South University (Approval No. 2021556). All experimental procedures were performed according to the ARRIVE guidelines and relevant regulations.

Author Contributions

J.Z was responsible for investigation, data curation, formal analysis, writing - reviewing and editing. D.Z was responsible for conceptualization, methodology, writing – reviewing and editing, supervision. X.L was responsible for investigation, data curation, methodology, formal analysis, writing – reviewing and editing. A.Z was responsible for funding acquisition, project administration, conceptualization, investigation, supervision, methodology, writing – reviewing and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Hunan Provincial Health Committee, China (Grant No. 202214052730), the Research Project on Education and Teaching Reform at Central South University (Grant No. 2024jy187).

Disclosure

Jiayi Zhao and Aiqun Zhu report grants from Hunan Provincial Health Committee during the conduct of the study. No other conflicts of interest has been declared by the authors.

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