

Circadian Rhythm, Exercise, and Heart

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Circadian rhythm is an evolutionarily conserved mechanism from archaea to human. To deal with the day-night changes in the environment on earth, circadian rhythm modulates the biological function to coordinate an appropriate timing for each process. Circadian rhythm and exercise have important impacts on each other. Exercise is a strong entrainment signal for mammalian circadian clock.¹ Proper exercise can have a significant circadian phase-shifting effect and affect the sleep and wake schedule in human.² Disruption of the circadian rhythm also has significant influences on the exercise function. The circadian gene *CLOCK* mutation in mice results in significantly reductions in muscle power and exercise endurance.³ Moreover, *CLOCK* mutation also disturbs muscle myofiber and mitochondrial functions.⁴ The close interactions between circadian rhythm and exercise are further strengthened by the findings that the diurnal variations of musculoskeletal functions and the impact of the circadian clock on energy metabolism and bone.⁵

The benefits of exercise to the heart is well-studied. Aerobic exercise reduces myocardial infarction and stroke risks by lowering blood pressure, reducing cholesterol level, and improving body weight control.⁶ The Harvard Alumni Health Study which began in 1962 with 17000 healthy male alumni has shown a direct relationship between exercise dose and mortality.⁷ The meta-analysis found that routine exercise produced a clinically favorable reduction in low-density lipoprotein cholesterol and increase in high-density lipoprotein cholesterol.⁸ Exercise training has a clinically significant benefit in blood pressure control with a 3 to 5 mmHg reduction in systolic blood pressure and 2 to 4 mmHg reduction in dia-

stolic blood pressure.⁹ The exercise dose required to decrease body weight appears to be significantly higher than the minimal dose required to have beneficial cardiovascular effects. Moreover, comprehensive lifestyle interventions, which include exercise, diet, and weight loss, are needed to prevent metabolic syndrome and diabetes mellitus.

Exercise induces the release of several myokines from skeletal muscle and adipokines from adipose tissues. In mice, aerobic exercise induces the production of irisin from muscle.¹⁰ The irisin promotes the conversion of white fat to brown fat in mice and probably in humans.¹¹ The levels of irisin are associated with chronic kidney diseases,¹² metabolic syndrome,¹³ and cardiovascular diseases.¹⁴ The macrophage colony-stimulating factor-1, which influences macrophage homeostasis, is also increased in skeletal muscle after exercise.¹⁵ With secretome analysis, various myokines are induced by acute exercise and exercise training.¹⁶ However, the exact roles of these exercise-related myokines are still under extensive studies and their physiological functions will shed lights on our understanding of cardiovascular diseases in the future. Based on these myokine discoveries, the influences of exercise are beyond body weight control, metabolism regulation, and blood pressure lowering. With the strong links between circadian rhythm and exercise, it is logical to assume that exercise can exert its beneficial effects on cardiovascular system through circadian modulation.

Cimen and colleagues observed that acute exercise resulted in depletions of energy charge, decreases of the adenosine triphosphate levels, and elevation of the malondialdehyde and 3-nitrotyrosine abundances of the rat heart tissue. These results indicated that acute intensive exercise could elevate oxidative stress and suppress anti-oxidant activity in the heart. Although abundant evidence supported the beneficial effects of exercise, excessive exercise indeed breaks the balances of energy utilization. Strenuous exercise increases the myocardial edema. Long-term marathon training is associated with

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myocardial fibrosis.¹⁷ The exact mechanism maintains the balance between exercise and myocardial protection or injury is still unclear. Cimen and colleagues further treated the increased oxidative stress in the heart after acute exercise with melatonin. Their data showed that melatonin is able to decrease the oxidative stress and recover the energy charge after acute exercise.

The melatonin is isolated in 1958 from bovine pineal. The synthesis and release of the melatonin are tightly controlled by the circadian clock and light exposure. Working as a major circadian hormonal output, the melatonin distributes temporal cues to the tissues with melatonin receptors. These melatonin signals synchronize the peripheral circadian clocks and provide feedback information back to the central circadian clocks in suprachiasmatic nuclei.¹⁸ Clinically, it is a reliable marker for circadian timing in human. The melatonin agonists are also used to treat circadian psychiatric and sleep disorders.¹⁹ The findings of Cimen and colleagues further extends the possible usages of these melatonin agonists to modulate exercise efficiency and cardiovascular diseases. These findings also connect circadian controls with exercise physiology modulations, which could have important impacts on the future therapeutic choices.

One key experiment in Cimen's studies²⁰ provides further insight into circadian and exercise relationships in the heart. After acute exercise, glutathione peroxidase, catalase, and superoxide dismutase activities are decreased and are recoverable by melatonin treatment. This observation implies that circadian rhythm is critical in the balance of the beneficial effects or the detrimental risks of acute exercise. It further enlightens us about the importance of the timing of doing exercise. Further exercise experiments in the circadian disruption animals or circadian gene knock-out mice are needed to confirm this hypothesis.

In conclusion, the strong links between circadian rhythm and exercise play important roles in the heart. We will need to take these two factors into consideration clinically. These timely and active links will provide new angles to the future therapeutics for the cardiovascular patients.

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DISCLOSURE

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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