Proceedings of ICBioMed 2024 Workshop: Computational Proteomics in Drug Discovery and Development from Medicinal Plants
DOI: 10.54254/2753-8818/74/2024.LA18907

Circadian Rhythm Disruptions and Their Impact on Acute Myocardial Infarction

Lin Wang

Department of Clinical Medicine, Xi'an Jiaotong University, 28 Xianning West Street, Xi'an, Shaanxi, China

linw1202@stu.xjtu.edu.cn

Abstract. Circadian rhythms refer to the roughly 24-hour cycle of physiological and behavioural changes in an organism that are regulated by the biological clock. In recent years, the influence of circadian rhythm on cardiovascular system has attracted wide attention. Acute myocardial infarction (AMI) is a disease of the cardiovascular system, which should not be overlooked, characterized by myocardial ischemic necrosis. Studies have shown that circadian rhythm disturbance can lead to a serious impact on the occurrence and development of AMI. Here, we highlight the relationship between circadian rhythms and the autonomic nervous system, inflammation, oxidative stress, cardiac remodelling and promising treatments. Understanding how these complex processes are interconnected is of critical clinical importance for optimizing treatment strategies and preventing the occurrence of AMI.

Keywords: Circadian rhythm, AMI, mechanisms, autonomic nervous system.

1. Introduction

Circadian rhythms are biological processes that follow a roughly 24-hour cycle, driven by the body's internal biological clock. These rhythms regulate various physiological and behavioral functions, influencing everything from sleep-wake cycles to metabolic processes. The circadian rhythm is composed of the central clock and the peripheral clock. The suprachiasmatic nucleus (SCN), located in the hypothalamus, is the most important component of the mammalian biological clock. The central biological clock plays a role in regulating the biological clock of various parts of the human body through nutriregulation and hormone regulation. The SCN is an autonomous oscillator and cycles even in vitro almost indefinitely [1], other tissues and organs in the body also have their own biological clocks, called peripheral clocks. Experiments show that retinal ganglion cells innervating the SCN are intrinsically photosensitive [2]. These external clocks are regulated not only by the suprachiasmatic nucleus, but also by the local environment. These environmental factors include not only light, but also other factors such as social conditions.

At the molecular level, circadian rhythms are controlled by a feedback loop involving key clock genes like BMAL1, PER, CLOCK, CRY. BMAL1, together with the transcription factor CLOCK or NPAS2, regulates the expression of other CLOCK genes [3]. In this feedback system, CLOCK and BMAL1 form a complex that activates the expression of PER and CRY genes, which later inhibit their own activity, forming a self-regulating cycle that aligns with the day-night cycle. Epidemiological studies have shown that circadian rhythm disturbances—caused by factors like shift work, irregular

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sleep patterns, or modern lifestyle habits—are increasingly linked to higher rates of cardiovascular diseases, metabolic disorders, and even cancer. For instance, shift workers exhibit a higher prevalence of hypertension, obesity, and heart disease, largely due to misalignment between their internal clocks and external demands.

Acute myocardial infarction(AMI), generally known as a heart attack, is characterized by the necrosis of myocardial tissue due to ischemia. Epidemiologically, AMI exhibits regional, age, and gender-based variations. The incidence of AMI is significantly higher in developed countries, which may be related to different lifestyles, climate and living standards. At the same time, AMI resolution is also increasing in developing countries, which may be related to lifestyle changes and inadequate medical care. Notably, individuals over the age of 65 face a significantly increased risk of AMI [4]. The age of onset of AMI tends to be younger, which is closely related to risk factors such as high mental pressure, excessive fatigue, smoking, insufficient exercise and obesity. Research suggests that the incidence of AMI exhibits temporal variation, with a higher occurrence in the morning hours, which may be linked to the body's circadian rhythms. This morning surge in AMI cases aligns with increased blood pressure, heart rate, and platelet aggregation during the early hours of the day—physiological processes regulated by the circadian clock. Circadian rhythm disruptions, caused by factors like shift work, irregular sleep patterns, and modern lifestyle habits, exacerbate the risk of cardiovascular events. For instance, studies indicate that shift workers are more prone to hypertension and heart disease due to misalignment between their internal clocks and external demands. The synchronization of the central clock in the SCN and peripheral clocks in cardiovascular tissues plays a crucial role in maintaining cardiovascular health. When these rhythms are disturbed, it can lead to increased susceptibility to cardiovascular conditions such as AMI. Understanding how circadian misalignment contributes to AMI pathogenesis can shed light on preventive strategies and potential therapeutic approaches aimed at restoring circadian balance to reduce cardiovascular risks.

This article aims to explore the intricate relationship between circadian rhythms and the pathogenesis of AMI, focusing on how disruptions in the biological clock may influence cardiovascular outcomes. Understanding these mechanisms can offer insights into optimizing AMI prevention and treatment strategies.

2. Mechanisms of AMI and the Role of Circadian Rhythms

AMI is a complex pathological event influenced by several biological mechanisms, all of which are intertwined with circadian rhythms. The body’s internal clock regulates key physiological processes such as inflammation, oxidative stress, and autonomic nervous system activity, which play crucial roles in the onset, progression, and recovery of AMI. Disruptions in circadian rhythms, caused by factors like irregular sleep patterns or shift work, can exacerbate these processes, increasing the risk of myocardial infarction and worsening outcomes after the event. By linking the inflammatory response, oxidative stress, and autonomic nervous system function to circadian rhythm regulation, researchers can better comprehend how disruptions to the biological clock increase susceptibility to AMI and contribute to adverse outcomes. Circadian misalignment, particularly heightened sympathetic activity during the day and reduced parasympathetic activity at night, plays a critical role in the progression of AMI, making circadian rhythm regulation a potential therapeutic target in cardiovascular disease managements.

2.1. Inflammatory response

The inflammatory response following myocardial infarction occurs in three stages: a hypoxia-induced apoptotic wave, a pro-inflammatory response, and an anti-inflammatory repair phase. Hypoxia triggers calcium iron overload in cardiomyocytes, activating proteases and apoptotic pathways that lead to widespread cell death, initiating a wave of apoptosis in surrounding healthy cells. This is followed by a robust pro-inflammatory response in which damaged cardiomyocytes release pro-inflammatory cytokines, reactive oxygen species, and damage-associated molecular patterns, recruiting immune cells such as neutrophils, macrophages, dendritic cells, and lymphocytes to the injury site [5]. In the final stage, inflammation subsides, and the repair process begins, characterized by myofibroblast proliferation,

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collagen deposition, scarring, and neovascularization, which help heal the injured tissue. However, an imbalance between the pro-inflammatory and anti-inflammatory phases can exacerbate acute myocardial injury and lead to adverse ventricular remodelling. Hypoxia stimulates angiogenesis in the infarct area, promoting endothelial cell proliferation and vascular dilation, which begins at the infarct margin and extends to the core, helping to reduce scarring and ventricular remodelling after myocardial infarction

2.2. Oxidative stress

The damage caused by oxidative stress in myocardial infarction occurs in two stages: the ischemia-reperfusion stage and the chronic remodelling stage. During ischemia, reduced oxygen supply to cardiomyocytes leads to increased mitochondrial reactive oxygen species (ROS) production, causing mitochondrial permeability changes and oxidative damage to key cellular structures. Upon reperfusion, the restoration of blood flow further enhances ROS production, which damages lipids, proteins, and DNA, impairing cell function. In the chronic remodelling phase following AMI, elevated ROS levels contribute to mitochondrial fragmentation and increased activity of monoamine oxidases, which degrade mitochondrial function. Neutrophils infiltrate the damaged heart tissue, producing ROS and chemokines that recruit dendritic cells and monocytes, creating a positive feedback loop [6]. This excessive ROS production leads to further damage to cellular components, perpetuating a vicious cycle of oxidative stress and mitochondrial dysfunction.

2.3. Autonomic nervous system and cardiovascular disease

Disruptions in circadian rhythms play a critical role in the development and progression of cardiovascular diseases, particularly by affecting the balance of autonomic nervous system activity, which in turn influences myocardial health and the risk of acute myocardial infarction.

Abnormalities in the cardiac sympathetic nervous system have been documented in myocardial infarction and have been directly implicated in pathogenesis and progression of MI [7]. The sympathetic nervous system is more active during the day. During the day, the sympathetic nervous system promotes an increase in heart rate, blood pressure and blood sugar levels, providing more energy for physical activity. When the sympathetic nerve is excited, it will increase the workload of the heart, so that the myocardium needs more oxygen, at this time, the ischemic hypoxia of the myocardium that is already in a state of hypoxia will be aggravated. Sympathetic nerve excitation can also cause coronary artery spasm, can also lead to myocardial ischemia and hypoxia. So sympathetic excitation increases the risk of heart attack.

In contrast, during the night, the activity of the sympathetic nervous system gradually decreases, and parasympathetic nervous system is more active, which helps the body enter a relaxed state and promotes the recovery and repair process. the parasympathetic nervous system promotes a slower heart rate, lower blood pressure, stable blood sugar levels, and promotes digestive and excretory functions. Disruptions in circadian rhythms, such as reduced sleep duration or decreased sleep quality, can shift this balance. Increased sympathetic nervous system activity and decreased parasympathetic function due to these disruptions may negatively impact cardiovascular health. Such imbalances can lead to heightened cardiovascular risk, contributing to conditions such as hypertension and increased susceptibility to acute AMI. Circadian rhythm disturbance can also disrupt cardiac remodelling after myocardial infarction by activating the sympathetic nervous system, thus causing changes in cardiac function and structure after myocardial infarction and promoting sympathetic remodelling. In addition, peripheral signals via SCN can directly affect the occurrence of cardiovascular diseases through the autonomic nervous system. At the same time, to regulate sympathetic nerve activity in the paraventricular nucleus can reduce the peripheral sympathetic nerve activity after myocardial infarction, thus reducing the induction rate of ventricular arrhythmia.

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3. Circadian Rhythm Disruptions and AMI Mechanisms

Circadian rhythm disruptions play a significant role in the pathogenesis of AMI by affecting various physiological processes, particularly through the autonomic nervous system. The balance between the sympathetic and parasympathetic nervous systems, platelet activity, blood pressure regulation, atherosclerosis progression, and cardiac remodelling are all influenced by the body's internal clock. Disturbances in circadian rhythms, such as those caused by irregular sleep patterns or chronic sleep deprivation, can shift the balance toward sympathetic dominance, heightening cardiovascular risk. This section explores how circadian rhythm disruptions lead to increased platelet activity and thrombosis, unstable atherosclerotic plaques, elevated blood pressure, and maladaptive cardiac remodelling, all of which contribute to the onset and progression of AMI.

3.1. Circadian rhythm and platelet activity

Platelet adhesion and activity also exhibit circadian rhythm fluctuations. The increased activity of the sympathetic nervous system in the morning enhances platelet activity and aggregation, promoting thrombosis. Contributing physiologic changes that exhibit a morning peak include arterial pressure, heart rate, and vascular tone, which promote plaque rupture, together with increased platelet reactivity and reduced fibrinolytic activity [8]. In the meantime, the frequencies of myocardial infarction and of sudden cardiac death are highest during the period from 6 a.m. to noon [9]. The platelet aggregability increases in the morning and the frequency of myocardial infarction also increases. This thrombosis can lead to the rupture of atherosclerotic plaques and trigger acute coronary events, such as myocardial infarction.

3.2. Circadian rhythm and atherosclerotic

Disruption of the circadian rhythm exacerbates the instability of atherosclerotic plaques. At night, the parasympathetic nervous system typically aids in cardiac tissue repair and promotes plaque stability. However, circadian rhythm disruption, especially chronic sleep deprivation or irregular sleep patterns, increases the secretion of inflammatory factors such as IL-6 and TNF-α, which weaken the fibrous cap of plaques and elevate the risk of plaque rupture and myocardial infarction. At the same time, experiments have shown that platelet dysfunction and hyperlipidaemia work in concert to aggravate atherogenesis [10]. Atherosclerosis is one of the important causes of myocardial infarction, which is characterized by the accumulation of cholesterol, calcium and lipids in the blood vessels, which will block the blood vessels and lead to myocardial ischemia and hypoxia. Platelets can be activated in response to endothelial injury, they can also interact with white blood cells to promote inflammation, and they can promote fibrosis of blood vessel walls. What's more, platelets can accumulate at the plaque damage and form blood clots, which can block blood vessels and cause heart attacks.

3.3. Circadian rhythm and regulation of blood pressure

Blood pressure fluctuates over time. Some researchers have observed that a pronounced and consistent reduction in the markers of sympathetic activity and an increase in those of vagal activity during the night [11]. These indicate that circadian rhythms can affect sympathetic nerve excitability, thereby reducing people's blood pressure by 10% to 20% during night sleep, resulting in a physiological phenomenon of low blood pressure at night and high blood pressure during the day. This is a normal physiological phenomenon. But when blood pressure does not drop enough at night, it can lead to persistent hypertension, and when blood pressure rises too quickly in the morning, blood pressure spikes, and the prevalence of cardiovascular disease increases.

Hypertension is one of the important factors of myocardial infarction. High bloodpressure can increase the burden on the heart, and the thickening of the heart muscle can affect the efficiency of the heart and eventually lead to heart failure. High blood pressure can also promote arteriosclerosis, and the damage to the artery wall will accelerate under the influence of high blood pressure, thus promoting the formation of atherosclerosis, which leads to reduced blood flow and coronary artery disease. High blood pressure also causes endothelial cell damage and increases the tendency for platelets to accumulate and

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clots to form, which occurs when clots block coronary arteries. When high blood pressure and other diseases interact, they collectively increase the new machine burden, increasing the likelihood of myocardial infarction. Therefore, changes in circadian rhythm can increase the risk of myocardial infarction by influencing blood pressure

3.4. Impact of circadian rhythm on cardiac remodelling

Cardiac remodelling, which occurs after myocardial injury, involves the replacement of damaged myocardial tissue with fibrotic connective tissue. This process is crucial for maintaining heart's normal shape and normal function, which can also lead to long-term deterioration of heart function. After the pro-inflammatory response is the repair stage of injury, scar tissue will be formed after wound healing to prevent myocardial rupture. Myofibroblast proliferation, collagen deposition and scarring, and directional changes in new blood vessels lead to wound healing. Circadian rhythms influence multiple aspects of cardiac remodelling, including inflammation, fibrosis, and cardiomyocyte metabolism, by regulating the timing and intensity of physiological responses. Disruptions in circadian rhythms, such as those caused by irregular sleep patterns or environmental stressors, can interfere with the natural repair processes of the heart.

During the healing process, circadian rhythms help orchestrate the transition from pro-inflammatory responses to the anti-inflammatory repair phase. This transition is crucial for preventing excessive fibrosis and scar formation, which, when dysregulated, can result in adverse remodelling. Myofibroblast proliferation, collagen deposition, and neovascularization follow a circadian pattern, and disruptions to this rhythm can lead to improper healing, excessive scar tissue formation, and changes in the heart's structure, such as ventricular dilation and wall thinning. These changes increase the risk of arrhythmias and reduce the heart's efficiency, leading to heart failure and a higher likelihood of recurrent myocardial infarctions.

Moreover, circadian misalignment affects blood pressure and metabolic processes, which further exacerbates the stress on cardiomyocytes. Elevated nighttime blood pressure, due to circadian rhythm disturbances, accelerates the maladaptive remodelling process, promoting the enlargement of the heart chambers and increasing the risk of ventricular arrhythmias. Overall, circadian rhythm disruptions not only impair the body's ability to effectively repair myocardial tissue but also exacerbate structural changes in the heart, leading to a greater risk of recurrent AMI and long-term cardiac dysfunction.

4. Promising Treatments of circadian rhythm in AMI

To mitigate the effects of circadian rhythm disturbances on MI and coronary heart disease, treatments should focus on improving sleep quality, regulating autonomic nervous system activity, and reducing oxidative stress. Interventions like cognitive behavioural therapy for sleep disorders and melatonin supplements can restore circadian balance, while β-blockers and calcium channel blockers help reduce sympathetic nervous system overactivity and myocardial oxygen demand, thus preventing coronary artery spasms and ischemia. Antioxidant therapies and statins help reduce oxidative stress and inflammation, supporting myocardial recovery after MI. Adjustments in lifestyle, such as maintaining regular sleep patterns and avoiding excessive nighttime light exposure, along with chronotherapy (timing medications like statins to align with the body's biological clock), can further optimize treatment outcomes and reduce the risk of cardiovascular events.

In addition to existing treatments, emerging therapies targeting circadian rhythms in the context of AMI hold great promise. Chronotherapy, which involves administering medications such as antihypertensives and statins at specific times of day to align with the body's natural rhythms, has shown potential in optimizing treatment efficacy. Research is also exploring the use of circadian clock modulators, such as REV-ERB agonists, to directly regulate the molecular components of the circadian system and improve cardiovascular outcomes. Some studies have pointed out that Rev-erbαprevented collagen/epinephrine-induced pulmonary thromboembolism and protected against microvascular microthrombi obstruction and infarct expansion in an AMI model [12], which plays an important role

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in the regulation of platelets, and also plays an important role in the cardiovascular system, especially myocardial infarction.

Furthermore, personalized medicine approaches, which tailor interventions based on an individual's unique circadian profile, could lead to more precise and effective treatments for AMI. Ongoing research into gene therapies targeting circadian-related genes may also open new avenues for preventing circadian disruption-related cardiovascular diseases. These innovative strategies, combined with lifestyle modifications and conventional therapies, may significantly reduce the burden of AMI and improve long-term patient outcomes.

5. Conclusion

Circadian rhythm disruptions have a profound impact on the autonomic nervous system, which plays a key role in the development of AMI. Abnormal sympathetic activation caused by circadian misalignment increases platelet activity, elevates myocardial oxygen demand, and worsens ischemia, all of which heighten the risk of AMI. Additionally, the disrupted circadian rhythm could also cause abnormal parasympathetic nerve excitation, affecting the stability of atherosclerotic plaque sex. At the same time, sympathetic nerve excitation causes abnormal increase in myocardial oxygen demand, which leads to ischemia and hypoxia of cardiomyocytes, exacerbating acute disease risk of MI. Improving sleep quality and maintaining regular rest patterns are essential preventive strategies. Furthermore, treatments aimed at restoring circadian balance and regulating autonomic nervous system activity offer promising approaches for reducing the risk and severity of AMI.

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