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Circadian rhythm disorder induced heart failure: Pathogenesis and therapeutics

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Abstract. Heart failure (HF), a complicated clinical illness with significant morbidity and mortality, high medical expenses, poor physical performance, and a low quality of life for patients, is defined by diminished heart function brought on by aberrant cardiac structure or function. The prevalence of HF is increasing rapidly. Circadian rhythm, night work, and sleep quality may all significantly affect the onset of heart failure. Numerous recent studies have demonstrated the tight relationship between circadian rhythm (CR) and the occurrence and management of heart failure.The association between CR and HF is still not fully understood,and there are also many gaps in the efficacy evaluation of circadian rhythm treatment in HF patients.This review improves our understanding of the pathogenesis of HF, further discusses the role of CR in HF, and provides insights into the prevention and treatment of HF. Finally, we explore the potential translational therapeutic approaches targeting circadian rhythms in patients with HF.

Keywords: Circadian rhythm,heart failure,Cardiovascular metabolism,circadian rhythm therapy, traditonal therapy.

1. Introduction

Circadian rhythm is a biological rhythm consisting of internal oscillations of approximately 24 hours, which synchronizes the internal functions of an organism with changes in the external environment. Mammals have a core clock and peripheral clocks that control their circadian rhythm. While the peripheral clocks are found in different tissues and organs, the central clock is located in the hypothalamic suprachiasmatic nucleus (SCN) [1,2]. By controlling the expression of target genes, peripheral clocks, which receive signals from the central clock, also contribute to local stability. Numerous studies have demonstrated that the biological clock is present in every cardiovascular cell and that circadian rhythm is a significant regulator of cardiovascular physiological function and illness [3,4].The adjustment function includes blood pressure, heart rate, heart contraction function and endothelial function, as well as the onset of acute myocardial infarction, arrhythmia, and heart failure [5,6]. During the day, the biological clock regulates heart contraction and metabolic activities, and maintains high heart rate and blood pressure, while the intensity of this physiological activities will be reduced at night [7].

However, with the widespread application of artificial light at night, the lifestyle of human life has changed significantly, such as shift work, time difference and staying up late will affect Circadian rhythm. Herrero et al. demonstrated that chronic circadian rhythm interrupts can cause changes in

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inflammatory factors abnormal reactions, lipid metabolism, and metabolic activities of related tissues (such as hypothalamus, liver, adipose tissue), including metabolism damage at the transcriptional level [8]. Furthermore, multiple investigations have demonstrated a favorable correlation between the incidence and exposure duration of cardiac disease and the degree of circadian rhythm disruption (CRD).Many physiological activities and functions of cardiovascular systems are regulated by the circadian rhythm. Long -term circadian rhythm disruption (CRD) can cause heart dysfunction, acute myocardial infarction, and then cause heart failure symptoms. At present, there is a lack of comprehensive understanding of the mechanism by which circadian rhythm disruption contributes to the pathogenesis of HF. Through some Pharmacological treatment (such as diuretics, renin-angiotensin System Inhibitors, vascular tensioner converting enzyme inhibitors) can alleviate the trend of heart failure, reduce the risk of cardiovascular death, and improve the prognosis of patients with heart failure. However, there are fewer clinical cases for using circadian rhythm therapy for HF patients, and there is a gap in treatment. The efficacy of circadian rhythm therapy also needs to be evaluated. Based on the literature reports in recent years, this review discusses the relationship between CR and HF. In addition, it also describes the potential conversion therapy for circadian rhythm, which provides insights on the treatment and control of heart failure diseases.

2. The Connection between CR and Heart Failure

2.1. Circadian Rhythm Disruption (CRD) Increase the Risk of HF

Heart failure (HF) is a disease caused by insufficient cardiac output due to the dysfunction of heart structure, which affects blood circulation and means that The heart is unable to provide for the body's fundamental metabolic demands. At present, there are currently more than 64 million people with HF worldwide, and its prevalence is increasing with an aging population and unhealthy lifestyles. Recent studies have found that circadian rhythm disruption (CRD) will increase the risk of adverse cardiovascular events, especially HF [9].Sleep is an important physiological process of the individuals, which has an important impact on the health of the brain and the normal operation of various organs of the body. Due to social and work demands, a considerable number of people in the world need to stay up late to work overtime or shift work, and short or poor sleep will affect health. At present, the common factors causing circadian rhythm disorder include staying up late and working at night. The resulting CRD can lead to the function damage of tissue and organ and metabolic disorders, thereby increasing the incidence of myocardial infarction, heart failure and other cardiovascular diseases [10,11].In a prospective clinical research involving 412 patients with myocardial infarction, it was found that events such as stay up late or shift work that disrupt the body's circadian rhythm can aggravate the myocardial injury and lead to long-term adverse reactions. Night work was linked to a 106% higher risk of heart failure and a 92% higher risk of significant adverse cardiovascular events throughout the span of the 5-year follow-up period. Furthermore, the findings were validated in animal models including mice and sheep. It was also found that the area of myocardial infarction in mice and sheep that simulate night work (that is CRD) was significantly higher than that in mice and sheep with normal circadian rhythm, further confirming that CRD can aggravate post-operative myocardial injury. Myocardial injury can cause the heart to fail to pump blood to other parts of the body, leading to symptoms of heart failure.

Circadian rhythm gene KO mice often have different myocardial diseases and affect metabolic pathways related to the cardiac compensation. CLOCK, BMAL1 and REV-ERBα are important regulatory factors for mammalia's circadian rhythm, which directly affect how the body's circadian rhythm functions normally. In mouse cardiomyocytes, knocking out the BMAL1 gene leads to the development of hypertrophic cardiomyopathy characterized by poor cardiac remodeling and enlarged cardiomyocytes, left ventricular hypertrophy, and increased serum BNP (brain natriuretic peptide) levels. Similarly, specific knockout of rev-erbα/β leads to impaired cardiac contractility and the development of dilated cardiomyopathy phenotype in mice. However, it can be alleviated by a combination of high-fat diet and insulin resistance [12].In the heart, rhythmic genes and proteins account for about 13% and 8% respectively[13,14], and play an important role in signaling pathways related to growth and

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metabolism [15,16]. The Kchip2 (voltage door control potassium channel) in cardiomyocytes is also rhythmic, regulating the balance of Na+ and K+ ions in cardiac tissue.[17]. The fatty acids and glucose levels in the heart of mice are also influenced by circadian rhythm changes, as the genetic expression fluctuations associated with the fasting/feeding cycle are synchronized [18]. Disrupting the heart clock in mice through gene knockout would have a significant impact on metabolic pathways, including glycolysis, fatty acid oxidation, and protein synthesis.

The ratio of REV-ERB to BMAL1 expression was discovered to be directly related to the heart's beating function in a study that involved transplanting failed hearts from patients with cardiomyopathy that was dilated. If this ratio is lower than normal, it will cause impaired left ventricular relaxation function and a higher incidence of mitral regurgitation, directly affecting the circulation and blood perfusion of other tissues and organs, which may later lead to heart failure and multi-organ dysfunction. This suggests a connection between the degree of heart failure and the change of the REVERB/BMAL1 rhythm in dilated cardiomyopathy [19]. Therefore, the absence of the biological clock may lead to a cardiomyopathy phenotype and further develop to heart failure. These animal experiments and clinical data provide another perspective to confirm the important role of CR in cardiac metabolism and the role of CRD in HF.

2.2. CRD Contribute to the Pathogenesis of HF

Previous reports have revealed that Rev-erbα/β, a key regulator of the circadian clock, plays an important role in cardiac metabolic rhythm in both animals and humans. There is a circadian rhythm to the Rev-erbα/β gene's expression and activity in the heart. The heart's expression of Rev-erbα/β has a particular periodic patterning, peaking during the daytime hours of the light phase and troughing during the nighttime hours of the dark phase. Rev-erbα/β has an effect in cardiomyocyte metabolism and affects the metabolism of fat and glucose by controlling the transcription of genes involved in cardiomyocyte metabolism. More specifically, fatty acid oxidation (FAO) is improved by high Rev-erbα/β expression during the day, but enhanced carbohydrate metabolism is linked to low expression at night. This temporal regulation helps cardiomyocytes adjust their metabolic patterns according to their energy demands and the availability of nutrients at different times. Mice that have Rev-erbα/β knocked out exhibit a disturbed cardiac metabolic rhythm, progressive dilated cardiomyopathy, and ultimately, fatal heart failure. Similarly, dilated cardiomyopathy and heart failure may be significantly impacted by CRD in the human heart [20]. These findings suggest that maintaining the normal function of the circadian clock in the heart is crucial for cardiac health, and HF and dilated cardiomyopathy may benefit from treatment of CRD. Therefore, therapeutic strategies targeting cardiac circadian rhythm and metabolic pathways may help improve prognosis in heart failure patients.

3. The Mechanism of CRD Effect on HF

3.1. The Mechanism of CR

The periodic variation in several physiological processes and organisms' living activities is known as the circadian rhythm [20]. The SCN of the hypothalamus controls circadian rhythm. Additionally, circadian rhythm is linked to the proper operation of several bodily physiological processes, including the management of hormone levels, immunological response, and metabolism in a variety of physiological activities [21]. The biological clock gene's molecular oscillation mechanism controls circadian rhythm at the molecular level. The circadian system in animals is made up of two parts: the central circadian system, which is found in the SCN, and the peripheral circadian system [22].The peripheral circadian system exists in multiple tissues and organs, and the synchronization and coordination of the central circadian system and the peripheral circadian system ensures the function of tissue circadian rhythm.

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3.2. The impacts of Normal CR on cardiovascular system

Cardiomyocytes, vascular smooth muscle cells, fibroblasts, and endothelial cells are among the cardiovascular cells that exhibit a circadian rhythm [23, 24]. This rhythm controls a number of physiological or pathological processes, like heart rate, blood pressure, and cardiovascular health [25, 26].In the vascular system, the signal transmission processes involving resident cells, thrombosis, vascular function and tension all require the regulation of the biological clock [27,28]. For example, in humans, blood pressure is controlled by circadian rhythm, characterized by an increase in blood pressure upon waking and a decrease during sleep at night, while the blood pressure pattern in rodents is the opposite [29]. There are different phases to the heart's metabolic activity as well. The oxidative metabolic process surges in the initial phase of the light cycle, potentially supplying enough ATP for the body's many functions. To get ready for sleep, the heart's metabolism shifts toward the synthesis of triglycerides and glycogen in the subsequent part of the light cycle. In the dark cycle stage, the metabolic center will shift to the protein turnover process, preparing for the normal operation of the tissues and organs after waking [30]. After specific knockout of the BMAL1 or CLOCK gene in mice cardiomyocytes, the circadian rhythm of cardiomyocytes becomes disordered, leading to changes in the synthesis of triglycerides and glycogen, as well as glucose oxidation [31,32]. These metabolic pathway disorders can cause major risk factors for cardiovascular diseases such as obesity and diabetes.

3.3. The Relationship between CRD and HF

3.3.1. Different subtypes of HF and the main features of HF

Based on the left ventricular ejection fraction (LVEF), heart failure can be classified into the following 4 categories. (1) **Heart failure with reduced ejection fraction (HFrEF)**: Its characteristic is that the LVEF is less than 40%. Patients usually have weak pumping ability of the heart, leading to pulmonary congestion and systemic congestion, which is a common type of HF. (2) **Heart failure with improved ejection fraction (HFimpEF)**: It refers to patients whose baseline LVEF is less than or equal to 40%, but after treatment, the LVEF is greater than 40% and increased by at least 10% compared with the baseline. Although the LVEF has improved, the myocardial function has not been fully restored. (3) **Heart failure with mildly reduced ejection fraction (HFmrEF)**: It's a new classification of HF that has recently emerged, specifically referring to patients with LVEF between 41% and 49%. Drugs used to treat HFrEF may be effective for these heart failure patients. (4) **Heart failure with preserved ejection fraction (HFpEF)**: This type of HF is characterized by an LVEF of usually greater than or equal to 50%, but with left ventricular structural or cardiac diastolic function function abnormalities.

3.3.2. Effects of CRD on HF

Cardiomyopathy, heart fibrosis, and systolic function impairment can occur in mouse models when the circadian rhythm is disturbed, which can eventually result in cardiovascular mortality[33,34]. A crucial gene that controls and preserves a healthy circadian rhythm, rev-erbα/β also contributes to the metabolism of fats and carbohydrates. The normal rhythm maintained by Rev-erbα/β in cardiomyocytes allows the cells to preferentially use lipids as fuel during the resting period. When the Rev-erbα/β gene was knocked out in mice cardiomyocytes, it was found that the circadian rhythm was disrupted. HF and dilated cardiomyopathy resulted from a substantial alteration in cardiac metabolism and a decrease in the capacity of cardiomyocytes to utilize lipids while at rest. Modern people's circadian rhythm is disturbed by the pervasive use of artificial illumination at night, which throws off the body's internal clock's coordination with the outside world. Among the population with insomnia or sleep disorders, their risk of cardiovascular disease increases[35]. Myocardial infarction, ischemic stroke, and HF are all connected to shift employment, and these conditions are significant causes of HF.[36,37]. Circadian clock disruption is directly linked to the pathophysiology of HF and subsequently to the deterioration of post-injury decompensation. When the external environmental clock is inconsistent with the internal clock, it may cause myocardial ischemic damage. On the contrary, heart failure and myocardial injury

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can cause core clock function to be destroyed, which would worsen the harm that core clock causes to the function of the heart.

4. Circadian Rhythm Therapy on Prevention and Treatment of HF

4.1. Non-pharmacological Therapy Improve HF Due to CR Effects

4.1.1. Light therapy

Light plays an important role in maintaining the body's balance, and night workers are more likely to have more serious heart problems than those who work during the day. Previous evidence has revealed that during heart surgery, strong light can protect the body from damage such as reducing the risk of heart ischemia, and can also accelerate the body's healing after surgery. When light signals enter the eyes, they are transmitted to the SCN. Strong light can stabilize the expression level of the PER2 gene and increase the content of adenosine, thereby blocking the electrical signals that cause irregular heart rhythms and producing a protective effect on the heart. Therefore, light therapy can further improve cardiac metabolism by regulating CR, and alleviate and assist in the treatment of HF.

4.1.2. Eating behavior improvement

Although restricting sodium intake is a commonly used nutritional therapy for heart failure in clinical settings, there is currently insufficient evidence to demonstrate that managing heart failure symptoms can be achieved by limiting sodium intake. According to the recommendations of international guidelines, the range of sodium restriction varies from <1500 mg/d to <3000 mg/d, which also reflects the lack of consensus on sodium restriction from the side currently. Large-scale trials are needed subsequently to confirm whether this practice can benefit the patients with HF, especially those with HFpEF. Regarding the prevention of heart failure, adjusting the diet pattern to the mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet may be helpful. The focus of the DASH diet is to add key nutrients beneficial to heart health (such as potassium, magnesium, and calcium) to the diet and limit the intake of added sugar and salt. Natural foods, lean meats, and healthy fats are highlighted in the Mediterranean diet. Compared with the DASH diet, the Mediterranean diet is more flexible in terms of food types and advocates moderate eating. strict compliance to the Mediterranean diet is correlated with a lower likelihood of HF and can improve HF, particularly the prognosis for individuals with acute compensated HF, in accordance to studies that show it can lower blood cholesterol levels and reduce the possibility of heart disease. However, there is currently inadequate research being done in this area; hence, more extensive and in-depth investigations are required in the future.

4.1.3. Exercise

Selecting the ideal time of day to workout might be beneficial. Due to skeletal muscle anomalies and cardiopulmonary deterioration, those suffering from heart failure typically have lower tolerance to physical activity and cardiorespiratory fitness (CRF).Especially for patients with HFpEF, appropriate exercise training can improve exercise tolerance, for example aerobic exercise can significantly improve VO_2 in HFpEF patients and improve the left atrial volume index of patients.

4.1.4. Others

When CDR can’t be avoided, for example during shift work, it can be mitigated by adjusting shift schedules or taking short naps during work hours, and regular meals [38]

4.2. Pharmacological Circadian Rhythm Therapy of HF

4.2.1. Small-molecule modifiers

Circadian rhythm therapy seems to be a promising emerging treatment strategy for heart failure, which may help adjust the cardiac biological rhythm, improve cardiac function and overall health status of

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patients. Recent research suggested that the biological clock can be manipulated to protect the heart [39]. After ischemia-reperfusion treatment was applied to wild-type mice, SR9009, a REV-ERB agonist, was used for treatment, and the results showed that due to the reduction of REV-ERBα and REV-ERBβ transcription-formed mRNA concentration and post-translational protein content by SR9009, the immune cell infiltration after injury was reduced, and cardiac function was improved, heart hypertrophy and infarction area were reduced, and the risk of heart failure was lowered [40]. Furthermore, by constructing the Transverse Aortic Constriction mouse model (TAC), which is a classic model used to explore myocardial hypertrophy and heart failure, it is noteworthy that when mice develop myocardial hypertrophy or heart failure, SR9009 can play a protective role in cardiac function. This suggests the significant effect of agonists in HF [41].Considering the differences or individual variability in biological clock regulation among different tissues or individuals, targeted drugs for specific circadian components may produce different effects due to different site of contact or pathways, therefore, the research on circadian rhythm therapy for HF is relatively limited and is still in the exploratory stage.

4.2.2. Angiotensin-Converting Enzyme Inhibitor(ACEI)

Time is a crucial factor in circadian rhythm therapy. While gender and syndrome of the patient are usually taken into consideration during the treatment process, the timing of the treatment is often overlooked. Many clinical studies on cardiovascular disease treatment also fail to mention the timing of drug administration [42]. For instance, high blood pressure usually occurs in the morning. However, in many cases, antihypertensive drugs are taken around 8 am in the morning. This time point leads to peak blood plasma levels of the drug during the day, when the most adverse reactions are likely to occur. ACEI lowers blood pressure and protects the heart by blocking the process of the angiotensin-converting enzyme (ACE) and decreasing the synthesis of angiotensin II. It is widely utilized to treat diabetes, heart failure, hypertension, and myocardial infarction recovery. Benazepril, Lamipril, and Enalapril are typical ACEI medications.

4.2.3. Diuretics

For heart failure patients, the optimal time for using diuretics is usually in the morning. On the one hand, as taken in person, diuretics often start working 1-2 hours later and climax 6-12 hours later, lasting 16-18 hours. Therefore, taking it in the morning can increase urine output during the day, help excrete toxins, and facilitate sleep at night when the effect wears off. On the other hand, taking diuretics once a day is similar to taking daily antihypertensive drugs, as the peak of blood pressure is during the day, and diuretics generally have a hypotensive effect. Taking medication in the morning can not only facilitate the hypotensive effect but also prevent low blood pressure at night. Conversely, taking diuretics at night can increase blood viscosity, which is prone to induce cardiovascular and cerebrovascular diseases, and can also increase urine output at night, affecting sleep quality. Therefore, for heart failure patients, taking diuretics in the morning every day is more suitable to achieve the best therapeutic effect and reduce adverse reactions.

5. Conclusion

Nearly every kind of cell in the cardiovascular and circulatory system has a circadian clock, and circadian rhythm controls several important physiological functions like heart rate, blood pressure, and metabolism. Furthermore, circadian rhythm is intimately linked to the onset, progression, and outcome of a number of cardiovascular disorders. On the other hand, CRD has a number of detrimental impacts on the heart and cardiovascular system metabolism, including changing metabolic pathways, resulting in significant susceptibility for cardiovascular illnesses (including diabetes, obesity, and myocardial infarction), and raising the chance of HF. The deeper mechanisms and significance of therapy and prevention treated with circadian rhythm for heart failure are still awaiting exploration and explanation. This review summarizes several kinds of circadian rhythm-based pharmaceutical and non-pharmacological treatments that have demonstrated promising results in the prevention and management of HF. Yet further research is required to determine how effective these treatments are for HF. It is

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necessary to create more novel strategies and techniques for treating HF. The medical care and lifespan of those with cardiovascular illnesses might be greatly enhanced by further extending the use of circadian rhythm therapy in clinical trials.

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