

The Role of Circadian Rhythm Disruptions in Cardiovascular Disease Progression: A Systems Biology Perspective

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Abstract

The circadian rhythms, controlled by endogenous biological clocks, play a central role in the maintenance of cardiovascular homeostasis by controlling processes like blood pressure, heart rate, vascular tone, and metabolic pathways. These rhythms are synchronized with the external environment by cues like light, so that physiological functions are in phase with the day-night cycle. However, the lives of modern man with his/ her adverse sleep schedules, shift duties, and increased exposure to artificial lights have led to wide circadian misalignment that greatly increases the risk of suffering from cardiovascular diseases. This review looks at the mechanisms involved in disruptions of circadian rhythms and CVD, which include autonomic dysregulation, metabolic derangements, increased inflammation, and oxidative stress. Dysregulation of the clock genes BMAL1 and CLOCK in the context of endothelial function and vascular health is also discussed. A systems biology approach to combine genomic, transcriptomic, and proteomic data is proposed as a holistic view of these interactions. Therapeutic strategies include lifestyle interventions like time-restricted feeding, pharmacological approaches like melatonin supplementation, and chronotherapy. These are able to decrease the negative impact caused by circadian disruptions. Instead, this review clearly states the research gaps by showing that multifaceted approaches are needed as well. This is stated because the maintenance of circadian rhythm is required for the prevention and management of CVD. This promising avenue of treatment for cardiovascular diseases, by integrating personalized medicine and biology systems, could simplify outcomes and lighten the burden across the world.

Keywords

Circadian rhythms, Cardiovascular diseases, Systems biology, Inflammation, Oxidative stress, Chronotherapy.

1. Introduction

Terms 'circadian rhythm' are terms that denote biological functions that run according to an internal approximate cycle close to 24 hours. Circadian rhythms regulate human and other animals' physiological and behavioral functions. Their primary regulator is the suprachiasmatic

nucleus in the anterior hypothalamus, or SCN, sometimes called the body's master clock. The SCN gets environmental cues, especially light, so as to harmonize the body's internal clock with external exposure, thereby orchestrating daily rhythms in metabolism, sleep-wake cycles, hormone release, and many other important physiological activities (Shin et al., 2017; Copertaro & Bracci, 2019). The working of circadian rhythms is profoundly based on molecular mechanisms integrating clock genes and proteins. These genes are expressed in nearly every cell, thus creating a network of peripheral clocks that can maintain rhythmicity even in the absence of external cues (Poggiogalle et al., 2018; Çakmur, 2018).

For example, the clock genes expression in the skin fibroblasts has been demonstrated to follow physiological and behavioral rhythms in humans; this suggests that these peripheral clocks are important in the regulation of local physiological activities (Wilkaniec et al., 2016; Spörl et al., 2011). The SCN interacts with peripheral clocks to regulate the movement of most body parts in harmony, coordinating changes in the environment that are predictable, such as that of light and darkness (Husse et al., 2014). Circadian rhythms do not only direct homeostasis but also metabolic processes to an optimal state. They also aid in the temporal separation of competing metabolic pathways, such as anabolism and catabolism, which enhances the efficiency of metabolism (Poggiogalle et al., 2018; Çakmur, 2018). Dysregulation of these rhythms has been a hallmark in shift workers or any individual who has an abnormal sleep schedule and has been reported to lead to a host of diseases, such as metabolic syndrome, cardiovascular diseases, and impaired cognition (Jagannath et al., 2017; Takeda & Maemura, 2010). For example, studies have proven that circadian rhythm disorders tend to relate to a high prevalence of heart diseases and organ damages in the patients suffering from hypertension (Zeng et al., 2019).

In addition, circadian rhythms influence other physiological processes including immune responses. Research has proven that immune cells, such as CD4⁺ T cells, have circadian fluctuations in their activity and composition that can affect how the body reacts to infections and inflammation (Bollinger et al., 2011). In addition, the timing of allergic reactions, such as asthma attacks, has been found to be often associated with the circadian clock, indicating that biological rhythms play a role in the timing of the immune response (Baumann et al., 2013). Circadian rhythms are important for the maintenance of cardiovascular health because they regulate many physiological processes that determine heart function and vascular dynamics. These rhythms are generated by internal biological clocks, which are coupled to external environmental cues, particularly the light-dark cycle. The master clock is located in the hypothalamus, at the suprachiasmatic nucleus SCN that guides and sets the entrainments of peripheral clocks in tissues, for example, the heart and blood vessels. This synchronization is required to optimize the performance of the cardiovascular system for both day and night cycles (Lin, 2024; Thosar et al., 2018).

The most crucial part that circadian rhythms play within the heart lies in heart rate, blood pressure, and myocardial contractility. Diurnal variations are found in both heart rate and blood pressure, such that peaks and troughs in these two phenomena coincide with activity and rest phases in the body. For example, blood pressure is higher during the early morning and lower during the night; the latter phenomenon has a very tight correlation with the circadian rhythms (Lecour et al., 2021; Young, 2003). Dysregulation of these rhythms may occur in a variety of individuals, including those working at different shifts or in occupations involving irregular sleep. These have been associated with higher cardiovascular risk, including hypertension and myocardial infarction, according to the studies of Tong et al., 2013, and Thosar et al., 2018.

In terms of genes, circadian rhythms also control cardiac function and metabolic gene expression. For instance, circadian clocks have a regulatory function on the expression of cardiac ion channel genes, that in turn could affect the electrical activity and contractility of the heart (Tong et al., 2013; Yaniv & Lakatta, 2015). Besides, it has been observed that the cardiac-specific circadian clock influences myocardial gene expression and transcriptional responsiveness to fatty acids as well as tolerance to ischemia/reperfusion, helping the heart to be prepared in time for responding to environmental pressures (Wu et al., 2011; Durgan et al., 2010). In this respect, this ability is important to protect the heart from undesirable effects during the time of stress, such as stress caused by physical exertion or emotional stress.

Circadian interaction with the autonomic nervous system is also an important determinant of cardiovascular health. It consists of two divisions, sympathetic and parasympathetic branches. It is in a cycle of periods with changes in its level of activity, affecting heart rate and vascular tone. Thus, the increase in sympathetic tone that develops throughout the day will result in higher cardiac output and blood pressure; at night, it increases the parasympathetic tone, promoting sleep and restoration (Lin, 2024; Thosar et al., 2018). Rhythmic regulation is important for the maintenance of homeostasis but for the prevention of pathological states that arise because of chronic stress or disturbance of the circadian system. Circadian rhythms also play a role in the regulation of endothelial function and vascular health. Circadian rhythms regulate the expression of thrombomodulin, an important regulator of coagulation, in vascular endothelial cells. Dysregulation of this clock-controlled gene may cause an imbalance in fibrinolytic and thrombogenic activities, thereby predisposing to thromboembolic events (Takeda et al., 2007; Man et al., 2021).

Besides this, the circadian clock affects the sensitivity of vascular smooth muscle cells to a variety of stimuli, which could influence vascular tone and resistance. This demonstrates that even more crucial circadian control is to cardiovascular wellness (Rudic, 2009; Thosar et al., 2018). The clinical implications of circadian rhythms in cardiovascular health are deep. Circadian rhythm disruption in many people is observed in individuals who work at night, as evidenced by higher prevalence of cardiovascular diseases in them than in daytime workers (Tong et al., 2013; Thosar et al., 2018). Such an association has emphasized the importance of strategies that aim to restore circadian alignment in the mitigation of cardiovascular risk. One new emerging area is timing of drug administrations with chronotherapies aiming at aligning with the biological clock to augment cardiovascular treatment outcomes and reduce its side effects (Jamal et al. 2023; Young 2003).

2. Mechanisms Linking Circadian Disruptions to Cardiovascular Disease

2.1 Impact of Circadian Rhythm Disruptions on Cardiovascular Disease Development and Progression

Circadian rhythm disturbances have increasingly become recognized as important causes of the initiation and progression of cardiovascular diseases. Circadian rhythms are intrinsic cycles that occur every 24 hours and regulate different physiological processes and are essential to maintaining cardiovascular health. When these are disrupted, usually in modern lifestyle patterns of shift work, erratic sleep patterns, and exposure to artificial light, the effects are profound and far-reaching (Sharma, 2024; Wulandari, 2021).

This mechanism through which circadian disruption promotes cardiovascular disease is most notably through disruption in blood pressure and heart rate homeostasis. The normal patterns of circadian rhythms dictate the predictable pattern of fluctuations in blood pressure, characteristically with nocturnal dipping at sleep. Such a dip can be lost in disruption of these rhythms, leading to sustained elevated blood pressure, or what is commonly termed as non-dipping hypertension, and majorly acts as a risk factor for cardiovascular events (Bollinger & Schibler, 2014; West & Bechtold, 2015). It has been proven that individuals with altered circadian rhythms, such as shift workers, experience higher rates of hypertension and secondary cardiovascular complications (Durgan et al., 2010; Bennardo et al., 2016).

Table 1: Mechanisms Linking Circadian Rhythm Disruptions to CVD.

Mechanism	Impact on Cardiovascular Health	References
Blood pressure regulation	Loss of nocturnal dipping pattern leads to sustained hypertension.	Bollinger & Schibler, 2014; Zeng et al., 2019.
Metabolic dysregulation	Circadian disruption leads to dyslipidemia and insulin resistance, contributing to atherosclerosis.	Poggiogalle et al., 2018; Csoma, 2023.
Inflammation	Elevated CRP and IL-6 levels worsen endothelial dysfunction and atherogenesis.	McAlpine & Świrski, 2016; Morris et al., 2017.
Oxidative stress	Free radical formation damages endothelial cells, promoting vascular dysfunction.	Trujillo-Rangel, 2024.
Autonomic imbalance	Increased sympathetic activity and decreased parasympathetic tone leads to arrhythmia and hypertension.	Morris et al., 2016; Chen & Yang, 2015.

In addition, circadian disturbances may result in changes in metabolic processes that are directly related to cardiovascular health. For example, circadian rhythm desynchronization leads to dyslipidemia, which is an abnormal lipid level in the blood, and one already established risk factor for atherosclerosis and coronary artery disease (Scheer et al., 2011; Peñaloza-Martínez et al., 2022). Circadian rhythm disruption is linked to the increase of pro-inflammatory cytokines and markers, such as interleukins, that may worsen endothelial dysfunction and support atherogenesis (Wulandari, 2021; Peñaloza-Martínez et al., 2022). Interactions of circadian rhythms with metabolic syndrome emphasize that stable sleep-wake cycles and the time to have meals would serve to facilitate the maintenance of cardiovascular health (Bae et al., 2019; Egan et al., 2017).

One significant application of the knowledge regarding the circadian modulation of inflammation pertains to its implications for the understanding and treatment of cardiovascular diseases. Circadian clocks regulate the expression of many immune-related genes and the activity of immune cells, which can influence the body's response to injury and inflammation (Niu, 2023; Egstrand et al., 2021). For instance, studies have established that the onset of MI follows circadian rhythms; there is a significantly higher incidence of MIs when platelet activation is at its peak in the morning hours (Scheer et al., 2011; Škrlec et al., 2019). That would most likely expose disturbance in circadian rhythm, which would usually support higher inflammatory responses and susceptibility to acute cardiovascular events. Moreover, circadian disruption affects an essential component of the autonomic nervous system, part of the

regulation of cardiovascular systems. Both sympathetic and parasympathetic branches of the autonomic nervous system exhibit diurnal variations and affect heart rate variability and vascular tone. Disturbances of such rhythms lead to autonomic balance, with increases in sympathetic drive and a concurrent decrease in the parasympathetic tone, associated with adverse cardiovascular prognosis (Bollinger & Schibler, 2014; Durgan et al., 2010). This derangement in the autonomic may contribute to some arrhythmia and other cardiological complications. Malnutrition and stress resulting from adverse lifestyle habits add to the already adverse effects of circadian disruption. In shift workers, disruption of circadian rhythm leads to irregular eating, one of the known risk factors for Metabolic syndrome and obesity, which are two major contributors to cardiovascular disorder (Bollinger & Schibler, 2014; Shanmugam et al., 2013). Such lifestyle consequences form a vicious cycle amplified further by physiological circadian misalignment effects.

There is actually great evidence relating circadian disturbance and cardiovascular disease; studies that revealed to possess even a more significant risk to populations, that are caused through circadian disturbance - these include, among others night shift workers - patients affected through a disorder of sleep (Durgan et al., 2010; Bennardo et al., 2016; Fatima et al., 2021). For instance, it has been observed that chronic circadian disruption is associated with higher rates of ischemic heart disease and poorer prognosis following cardiovascular events (Bennardo et al., 2016; Peñaloza-Martínez et al., 2022). This makes the regulation of circadian rhythm an important necessity to prevent cardiovascular diseases, thereby implying interventions intended to once again align the circadian rhythm can be useful.

2.2 Circadian Misalignment Affects Molecular and Cellular Pathways in the Cardiovascular System

The disruption of most of the molecular and cellular processes that maintain cardiovascular health has led to a profound effect of circadian misalignment on the cardiovascular system. Importantly, it is a circulating clock supervising the supra-chiasmatic nucleus that primarily controls circadian changes; through it, such varied physiological processes become coordinated, including blood pressure, heart rate variability, and vascular function. When such rhythms are deranged, like in shift workers or irregular sleepers, this would lead to enhanced cardiovascular risk and disease progression, it has been postulated (Morris et al., 2017; Morris et al., 2016).

One of the most vital pathways that appear to be modified by circadian misalignment is the inflammatory response. The elevation of inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), has been shown to be connected to an grew risk of cardiovascular disease; disruption of circadian rhythms elevates these markers (Morris et al., 2017; Morris et al., 2016). For example, Morris et al. showed that chronic shift workers have increased levels of hs-CRP and blood pressure because of circadian misalignment, thus, inflammation mediates the cardiovascular risk factors (Morris et al., 2017). This will cause endothelial dysfunction, a precursor to atherosclerosis and other cardiovascular diseases (Peñaloza-Martínez et al., 2022; McAlpine & Świrski, 2016).

Moreover, circadian misalignment also affects neurohumoral mechanisms regulating cardiovascular functions. Both sympathetic and parasympathetic components of the autonomic

nervous system display circadian variation by change in heart rhythm and vascular tone with day-night changes. Rhythmic disturbances were associated with increased sympathetic and depressed parasympathetic tone that favor increased heart rates and blood pressures (Morris et al., 2016; McAlpine & Świrski, 2016). This autonomic imbalance is one of the major contributing factors in developing hypertension and further complications related to the cardiovascular system. (Morris et al., 2016; Peñaloza-Martínez et al., 2022). BMAL1 and CLOCK are one of the significant molecular clock genes that are in charge of managing cardiovascular physiology. Disrupted these genes, alterations in gene expressions related to vascular function and metabolism occur. For instance, the ablation of BMAL1 is implicated in reduced vascular contractility rhythms and enhanced arterial stiffness that is linked with increased hypertension and cardiovascular disease (Chen et al., 2019). Moreover, circadian dysregulation of microRNA such as miR-103 impairs its downstream calcium signaling that is used by the contraction mechanisms of vascular smooth muscle cells (Chen et al., 2019).

Circadian misalignment affects lipid metabolism and is known to cause dyslipidemia, a well-established risk factor for cardiovascular disease. The disruption of circadian rhythms alters expression of lipid metabolism-related genes, thereby causing high levels of triglycerides and LDL cholesterol (Csoma, 2023). Such an imbalance may foster the progression of atherosclerosis and other cardiovascular diseases (Csoma, 2023). Lastly, circadian rhythm and its association with the metabolic pathways highlight the significance of the rhythmic sleep-wake cycle in preserving cardiovascular health (Roth et al., 2023). However, oxidative stress is one of the other significant mediators associated with misaligned circadian rhythms. The alignment of circadian rhythms leads to oxidative stress, more so than that allows free radicals to form and damage endothelial cells, resulting in vascular dysfunction (Trujillo-Rangel, 2024). Oxidative stress and inflammation together synergistically increase the risk for cardiovascular disease since their processes are interlinked, and their increase can induce each other (Trujillo-Rangel, 2024). Greater oxidative stress may be contributing to the increment of pro-inflammatory cytokines; such a cycle further advances cardiovascular disease, according to McAlpine & Świrski in 2016. Lastly, the gut microbiome also bears a relation towards circadian disruption and cardiovascular diseases. Circadian disruption has indeed been reported to change the compositional gut microbiota, known to be allied with systemic inflammation and metabolic derangement (Voigt et al., 2016; Voigt et al., 2014). The gut microbiome influences the production of short-chain fatty acids and other metabolites that can influence cardiovascular function (Voigt et al., 2016; Voigt et al., 2014). Hence, circadian misalignment may indirectly affect cardiovascular disease by affecting composition and function of the gut microbiota (Voigt et al., 2016; Voigt et al., 2014).

3. Systems Biology Approach

3.1 Improved understanding of circadian disturbances and CVD: a view from systems biology

The biological systems affected by circadian disturbance have been examined, along with the biological processes and molecular pathways that interact with other elements found in an ecological setting. This will assist researchers in gaining insight into how circadian rhythms impact cardiovascular health at the different levels from cellular mechanisms to systemic interactions thus clarifying, at last, the intricate interplay between circadian misalignment and risk for CVD (Poggiogalle et al., 2018; Wulandari, 2021). The circadian rhythm controls thousands of genes about cardiovascular function, metabolism, and inflammation. For example, BMAL1 and CLOCK are core clock genes that have been proved to mediate the central clock

regulation. It controls rhythmic expression patterns for genes, for instance, mediating vascular tone, heart rate, and blood pressure (Yusifova et al., 2023).

This shift in rhythms leads to a shift in the gene expression profile, which would result in an inefficient function of the cardiovascular system and susceptibility to disease. For instance, knockout of BMAL1 in cardiac muscle cells leads to hypertrophy and fibrosis that implies circadian regulation is nearly extremely crucial for cardiac health, thereby demonstrating that disruption of circadian cycles can cause pathological change in the cardiovascular system due to such gene networks and their interactions often identified by systems biology approaches (Yusifova et al., 2023; Wallach & Kramer, 2015).

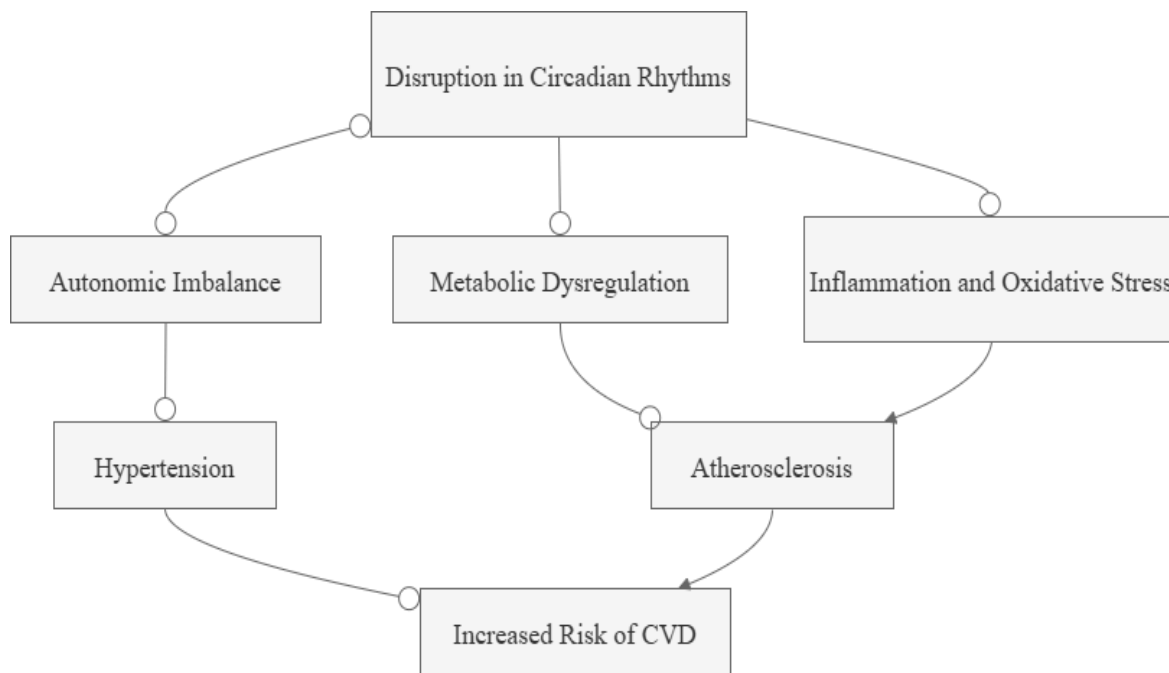


Figure 1: This demonstrates the pathophysiological mechanisms that associate disruption of the circadian rhythm with a higher risk of cardiovascular disease.

Circadian misalignment also has ramifications on very closely related metabolic processes that are in turn directly intertwined with cardiovascular health. Circadian rhythm disruptions may cause dysregulation of glucose and lipid metabolism, thus contributing to obesity, insulin resistance, and dyslipidemia, which are all major risk factors for CVD (Poggiogalle et al., 2018; Li et al., 2020). For instance, Poggiogalle et al. demonstrated that circadian misalignment negatively impacts glycemic control, thereby causing increased postprandial glucose levels (Poggiogalle et al., 2018). By using a systems biology approach, researchers can better model these metabolic pathways and how they interact with circadian rhythms, thus enhancing the understanding of how metabolic dysregulation causes cardiovascular disease.

Another critical area influenced by circadian rhythms is inflammation, where its dysregulation is highly associated with CVD development. Circadian disruption has proven to be involved with increased inflammation markers, specifically interleukin-6, and C-reactive protein to exacerbate the endothelial dysfunction caused by the disturbance and contribute to atherogenesis; this is true according to (Wulandari, 2021, Morris et al., 2016). This will allow the exploration of inflammatory pathways that are impacted by circadian misalignment and how

such processes might interact with metabolic and cardiovascular pathways in determining the course of disease. This integrative approach may therefore help identify some potential therapeutic targets for mitigating the inflammatory responses associated with circadian disruption (McClean & Davison, 2022; McAlpine & Świrski, 2016). The circadian rhythm also plays a critical role in the autonomic nervous system and cardiovascular health. The sympathetic and parasympathetic branches have diurnal variations that affect heart rate and vascular tone. Disruption of these rhythms leads to autonomic imbalance, characterized by increased sympathetic activity and decreased parasympathetic tone, associated with adverse cardiovascular outcomes (Chen & Yang, 2015; Mohandas et al., 2022). With the use of systems biology tools, researchers can model the interactions between circadian rhythms and autonomic regulation, which would provide insight into how these factors contribute to the pathophysiology of CVD.

From the system's biology perspective, environmental exposure to light and irregular sleep patterns are also of great importance in regulating circadian rhythms in addition to generally affecting cardiovascular health. For instance, work at night, or any kind of shift working, and other forms of sleeping irregularly cause chronic circadian misalignment linked to increased risks for cardiovascular diseases (Niu, 2023; Xu et al., 2023). Understanding how external factors interact with biological systems could inform public health strategies to lessen the impact of circadian disruption on cardiovascular health. A systems biology approach could integrate data across genomic, transcriptomic, proteomic, and metabolomic levels in describing the effects of circadian disruption on cardiovascular health. For example, systems biology has used transcriptome and proteome analyses to elucidate circadian parameters in tissues and has thereby shown how systemic changes predisposing individuals to cardiovascular diseases are precipitated by such disruption (Wallach & Kramer, 2015; Carrasco-Benso et al., 2016). Such an extensive understanding will contribute to the design of individualized interventions intended to correct circadian desynchronization and improve cardiovascular health.

3.2 Computational Models and Analytical Tools in Systems Biology Approaches

Most outstanding was the modeling using mathematics and then simulating how circadian rhythms would affect the physiological processes. An example would be the work done by Scheff et al. who put up a model of how circadian variability in inflammatory responses would interconnect, suggesting the importance of appreciating the role of inflammation as it exhibits diurnal variability for the therapeutic interventions of the diseases Scheff et al. (2010). This model shall allow for a number-based estimate of the modification of the inflammatory mediators due to the circadian cycle, which becomes indispensable for computing and clinical correlation. A third important tool could be systems biology approaches that merge multi-omics data, along with genomics, transcriptomics, proteomics, and metabolomics, during the analysis for determining the effects of circadian disruptions on cardiovascular health. This allows one to be able to elaborate on such involved models based upon the complex interactions between circadian rhythms and various other biological pathways involved in cardiovascular disease. It's evident where Morris et al showed through chronic shift works that circadian misalignment contributes to inflammation markers and the raised blood pressure thus proving a risk factor for circadian misalignment in human cardiovascular disease, Morris et al., 2017; Morris et al., 2016. The findings can be assimilated into the systems biology model to identify a potential therapeutic target and inform on the personalized therapeutic strategy.

Another broad area of use of computational tools in the study of circadian rhythms and cardiovascular health includes agent-based modeling and network analysis. They make it possible to model the response of individual cells or molecules to perturbations in a much larger biological context, thereby illustrating how circadian disruption leads to systemic changes, making an organism prone to diseases like cardiovascular diseases. For example, Papagiannakopoulos et al. studied the role of the lung's circadian rhythm tumorigenesis, illustrating the contribution of mutated circadian clock genes in tumor development (Papagiannakopoulos et al., 2016). While the study focuses on cancer, it will bring more relevance to disruptions in circadian rhythms and health.

Studies on clinical data and animal models generate large datasets that are analyzed using approaches in bioinformatics to determine the patterns and correlations existing between circadian rhythms and cardiovascular health. For instance, a systematic review conducted by Khan et al. has found that circadian variations of melatonin, which is inversely related to cardiovascular events, implies the possible existence of potential biomarkers for cardiovascular risk in disrupted circadian rhythm (Khan et al., 2020). Using bioinformatics tools to investigate such relationships can lead to the discovery of new biomarkers associated with cardiovascular risk due to disruptions in circadian rhythm. Use of Circadian Rhythm Data for the Prediction of Cardiovascular Outcomes: This area has dramatically increased use over the years; machine learning algorithms are utilized for complicated analysis, detecting patterns which even traditional statistical analysis may miss. For example, Chen et al. Such proposed applications of machine learning can help in quantifying the link between circadian misalignment and cardiometabolic diseases since such approaches could aid in better understanding the pathophysiology of such diseases, as proposed by Chen (2024). Predictive models that have been developed using machine learning can be informative in clinical decision-making and risk assessment.

4. Impact of Lifestyle Factors:

4.1 Shift Work and Circadian Disruption

Most life-style factors leading to disruption in circadian rhythm are associated with shift work, where circadian misalignment emerges due to being out of biological clock in individuals working odd-hour jobs from a synchronization point with environmental stimuli. Such incoordination has been linked to various adverse health effects, for example, increased susceptibility to hypertension, myocardial infarction, and metabolic syndrome (Kervezee et al., 2018; Fatima et al., 2021). At least in part, the metabolic and cardiovascular effects of shift work are moderated by the disturbances in sleep, as well as the epigenetic changes created by the shift worker's alteration in sleep-wake and feeding patterns. Of course, further, shift work has been recognized to be positively associated with inflammation markers, with direct correlation of elevated risk for cardiovascular disorders (McAlpine & Świrski, 2016).

4.2 Sleep Patterns and Cardiovascular Health

Regulation of the circadian cycle is very linked with sleep. Poor quality of sleep and reduced time spent in sleeping are mostly known to cause problems in circadian rhythm, resulting in negative impacts on cardiovascular conditions. For example, it has been noted that sleep loss

impairs endothelial functions and increases the blood pressure in a human system, thus posing as risk factors for CVD (Buxton et al., 2012; Lange et al., 2010). Buxton et al. showed that prolonged sleep deprivation plus disrupted circadian conditions result in disastrous metabolic consequences involving impaired glucose metabolism with increased insulin resistance, which can further heighten risks to cardiovascular disease (Buxton et al., 2012). Furthermore, Wulandari asserts that sleep disorders like insomnia and obstructive sleep apnea considerably increase the risk of cardiovascular diseases because they may alter physiological mechanisms responsible for the regulation of blood pressure and heart rate variability (Wulandari, 2021).

4.3 Diet and Circadian Rhythms

Dieting is also a lifestyle factor that impacts circadian rhythms and cardiovascular health. The synchronization of peripheral clocks in different tissues, such as the heart, is influenced by the timing and composition of food intake. Paula et al. have shown that dietary patterns, especially those that include high-fat diets, alter circadian rhythms by shifting the expression of clock genes and disrupting metabolic processes (Paula et al., 2022). High-fat diets may prolong the circadian activity period and disrupt feeding behavior rhythmicity, thus leading to obesity and associated cardiovascular conditions (Pendergast et al., 2013). Moreover, Yokoyama et al. demonstrated that a diet of high salt/high fat intake disrupts circadian locomotor activity and glucocorticoid synthesis and thus impacts cardiovascular health (Yokoyama et al., 2020).

Again, the gut microbiome is involved in the diet-circadian rhythm relationship. Circadian rhythm disruption has been shown to be associated with an imbalance of microbiota, which is shown to increase inflammation and cardiovascular disease (Voigt et al., 2016; Marques et al., 2017). Voigt et al. shows that a high-fat diet causes changes in gut microbiota composition that affect metabolic health as well as cardiovascular risk (Voigt et al., 2014). This interplay between diet, circadian rhythms, and the gut microbiome points to dietary choice as playing an important role in maintaining cardiovascular health.

5. Therapeutic Interventions:

5.1 Lifestyle Changes

Perhaps the best antidote against the circadian rhythm is lifestyle. As Kervezee et al. observed, sleep schedule consistency, along with an unchanged sleep-wake cycle, restores the circadian rhythm (Kervezee et al., 2018). Controlled exposure to light during work hours with minimal during sleep hours will be one such lifestyle changes experienced by shift workers. Good sleep hygiene, along with a dark, cool, and quiet sleep environment, enhances the quality of sleep and also promotes circadian regulation (Kervezee et al., 2018). The management of circadian rhythms as well as cardiovascular health involves some dietary interventions. It is assumed that the timing of food intake may affect the circadian rhythm, whereas unhealthy eating behaviors been connected to metabolic dysregulation and elevated risk for cardiovascular diseases (Mentzelou et al., 2023). Time-restricted feeding or aligning the timing of eating with the body's natural circadian rhythm may be useful in enhancing metabolic health and attenuating some risk factors for cardiovascular diseases (Mentzelou et al., 2023). In addition, it will safeguard the cardiovascular system diet high in antioxidants through oxidative stress reduction or inflammation with high intake diets like melatonin-based diets (Mentzelou et al., 2023; Wulandari, 2021).

5.2 Pharmacological Interventions

In recent times, the approach involving pharmacological, circadian-based drugs has evolved and has now gained favor as the appealing therapeutic technique meant for cardiovascular risk prevention. Melatonin, the sleep-wake cycle hormone, was shown to possess protective effects against cardiovascular health by virtue of its antioxidant action (Mentzelou et al., 2023; Wulandari, 2021). The supplementation of melatonin could be useful for the improvement of blood pressure regulation and prevention of cardiovascular events, especially in cases of disrupted circadian rhythms (Mentzelou et al., 2023; Wulandari, 2021). Furthermore, the identification of drugs that are already in use and can modulate circadian rhythms provides a promising new area of therapeutic intervention. Tamai et al. did, however, show that repositioning some drugs, such as antihypertensive agents, for modification of their circadian phase-shifting action may improve circadian regulation and then cardiovascular outcomes (Tamai et al., 2018). Such pharmacological strategies aimed at the clock may help in recovering normal physiological rhythms and mitigate the adverse effect of disruption in circadian rhythmicity on cardiovascular health.

5.3 Chronotherapy

Yet another promising application in the cardiovascular health arena is chronotherapy, or giving certain drugs at the exact time when those specific body processes are most active. According to Chen and Yang, such therapy could be effective in the treatment of hypertension and other cardiovascular conditions because the same drug can significantly vary in its efficacy at one point or another (Chen & Yang, 2015). For instance, certain antihypertensive drugs should be given at certain times of the day in synchronization with the natural peak and trough of blood pressure, which is regulated by circadian rhythms (Chen & Yang, 2015; Zhang et al., 2021).

5.4 Circadian Clock Targeting

Recent studies were focused on circadian clock mechanisms as a target for therapeutic application in CVD. Man et al. opined that by understanding the circadian regulation at a molecular level within the vascular system, novel approaches to the prevention and treatment of CVD would be unmasked at the molecular levels (Man et al., 2021). In particular, it has aimed at specific interventions on clock genes or pathways leading to a normal circadian rhythm and thus an attenuation of risk for cardiovascular pathology.

5.5 Behavioral and Environmental Interventions

Behavioral interventions include the practice of more frequent healthy and regular physical activities that influence circadian patterns toward good heart health. Exercise also has the ability to alter sleep positively. In addition, it serves as a procedure that resets the clock to work correctly as regarding the cardiovascular activity as mentioned in Poliwczak et al. (2019). On top of these, environmental measures assist an individual to rectify the circadian rhythm by steering clear of nocturnal artificial lighting and maximizing daytime illumination (Poliwczak et al., 2019).

Table 2: Pharmacological Approaches and Challenges in Targeting Circadian Rhythm Disruptions.

Topic	Details	Citations
Role of Pharmacological Agents		

Lithium	- Influences the amplitude and period of the molecular circadian clockwork. - Stabilizes mood and improves circadian alignment. - Valuable in managing mood disorders with circadian disruptions.	Li et al. (2012); Sanghani et al. (2020); Gold & Kinrys (2019)
Melatonin	- Regulates sleep-wake cycles. - Effective for delayed sleep phase disorder and shift work disorder. - Improves sleep onset and quality. - Reduces cardiovascular risks from sleep deprivation and circadian misalignment.	Zee et al. (2013); Peng et al. (2022); Sulli et al. (2018)
Wake-Promoting Agents	- Modafinil and armodafinil counteract excessive daytime sleepiness. - Enhance alertness and cognitive function. - Reduce the impact of circadian disruptions on health and daily activities.	Zee et al. (2013)
Challenges in Clinical Practice		
Individual Variability	- Genetic differences, comorbidities, and lifestyle factors affect drug response. - Some individuals may show intolerance or non-responsiveness to lithium, requiring alternatives.	Ayyar & Sukumaran (2021); Abbott et al. (2019); Gold & Kinrys (2019); Federoff et al. (2021)
Timing of Administration	- Efficacy depends on proper timing aligned with circadian rhythms. - Incorrect timing of melatonin may worsen circadian misalignment.	Lee (2023)
Side Effects and Drug Interactions	- Melatonin may cause drowsiness, dizziness, and hormonal effects. - Lithium requires monitoring due to potential toxicity and interactions, especially in patients with renal impairment.	Peng et al. (2022); Sulli et al. (2018); Gold & Kinrys (2019); Sanghani et al. (2020)

6. Research Gaps and Future Directions:

6.1 Limitation of previous works done on Circadian Rhythm and Cardiovascular disease

6.1.1. Methodological limitations

Among methodological issues facing circadian rhythm research is study heterogeneity concerning designs and methods. Most use different definitions to describe circadian disruption,

make measurements by means of various techniques, and collect information from populations made up of vastly different individuals. This heterogeneity makes it complicated to compare findings from various studies (Yu et al. 2023; Wulandari, 2021). For example, whereas some articles focus on how shift work relates to the overall effect on the heart, others study other subjects like the effects of sleep disorder or even the way of nutrition (Khan et al., 2020; Poliwczak et al., 2019), a challenge toward creating uniform findings and conclusions. For this reason alone, it is impossible to create a generalization for later study and clinic settings.

Moreover, most experiments rely on self-reported information about sleep behavior, dieting, or other lifestyles, which introduces biases and inaccuracies that manifest in the results (Tamai et al., 2018). Others require objective measurements, such as actigraphy or polysomnography, which most often are provided by much smaller sample sizes depending on the available resources, raising the issue of generalization (Yau & Haque, 2019). Furthermore, the application of circadian rhythms using animal models may not reflect the nuances of human biology, which would be a likely source of divergence in translation to clinical practice (Lewis et al., 2018).

6.1.2. Knowledge Gaps

Even as literature piles up, huge gaps exist in the mechanisms that relate circadian rhythms with cardiovascular health. For example, there is evidence of the fact that circadian disruption can raise the likelihood of cardiovascular diseases; however, the molecular mechanism and genetics behind it are not well explained (Lecour et al., 2021; Niu, 2023). In this regard, the findings indicate that the study has already identified the role of circadian clock genes in the control of cardiovascular functions but further studies on their interaction with the environmental triggers of diet and light are needed (Mohandas et al., 2022; Wang et al., 2019). This is an exciting area of focus concerning the function of the gut microbiome in mediating circadian influences on cardiovascular health, with still early research in this area (Peñaloza-Martínez et al., 2022; Estarlich et al., 2022). Understanding how circadian rhythms influence gut microbiota composition and function and the latter's effect on cardiovascular health can provide leads on potential therapeutic targets.

6.1.3. Translational Issues

Translation of the findings of research into clinical practice is yet another great challenge. Melatonin and lithium stand at the top of the pharmacological agents most used to regulate circadian rhythms leading to better cardiovascular outcomes; however, practical use is still hindered by the difference between individuals in response and side effects (Bae & Androulakis, 2018; Škrlec et al., 2021). Another is the timing of drug delivery in relation to circadian rhythm, which may be considered an important requirement to improve the efficacy of therapy but is often overlooked in practice (Mistry et al., 2020). Finally, the current clinical guidelines regarding the treatment of cardiovascular disease do not consider circadian rhythms. Most healthcare providers will not be educated on the aspect of circadian rhythms concerning cardiovascular health, and patients, therefore, miss opportunities in education and potential intervention (Man et al., 2021; Leng et al., 2019). Standard guidelines developed for

standardizing circadian considerations in the management of cardiovascular diseases would improve the outcomes of a patient and hence reduce the CVD burden.

6.2 Future Research on Circadian Disturbances and Cardiovascular Diseases

6.2.1. Mechanistic Studies

Establishing molecular and cellular mechanisms as to how disturbances in the circadian are related to cardiovascular health would be studied in the future. For example, then, studies like Reitz et al. on how circadian pharmacology influences the inflammasome could be extended to find out how circadian rhythms regulate inflammatory pathways in a variety of cardiovascular-related conditions Reitz et al. (2019). Knowledge of the exact routes in molecules engaged in circadian regulation of cardiovascular function will help reveal how such disturbances contribute to disease progression.

The role of the gut microbiome in mediating the effects of circadian disruptions on cardiovascular health should also be studied. For example, the type of studies would include those conducted by Guo et al. regarding the effects of dietary polyphenols on circadian rhythms and gut microbiota that could be an information source related to the hypothesis that diet-related interventions may diminish cardiovascular risks as a result of circadian misalignment (Guo et al., 2019). These kinds of studies may come to identify innovative therapeutic targets involving circadian rhythmicity in conjunction with enteric microbiome and cardiovascular functions.

6.2.2. Longitudinal and Interventional Studies

Some studies of temporal courses, within and related to cardiovascular health endpoints on circadianity, are fundamental in determining causal pathways. The future longitudinal study should be performed among populations with high risks of circadian disruption risks, such as shift workers, to assess the long-term effects of cardiovascular health due to circadian misalignment. For example, the Fatima et al. study would prove helpful for further studies with broader scopes to look for increased dangers for cardiovascular disease in the population working shifts (Fatima et al., 2021). The interventions that are recommended with lifestyle modification with time-restricted feeding or chronotherapy must be carried out for their impact on circadian rhythm and cardiovascular outcome. For instance, the hope that time-restricted feeding might serve as a therapeutic strategy to counteract circadian rhythm disruption to improve metabolic health is provided by Roth et al. Therefore, this type of research is necessary for CVD as suggested by Roth et al., 2023. The outcomes may provide evidence for the treatments that the healthcare providers would prescribe to their patients with a propensity for CVD.

6.2.3. Pharmacology studies

Research studies must continue investigating the discovery and use of drugs for modulation of circadian rhythms. Tamai et al. reported existing drugs that could modulate circadian clocks, which may serve as a candidate for repositioning in the treatment of cardiovascular diseases (Tamai et al., 2018). Future research should be done based on efficacy and safety among the population with a focus on the cardiovascular disease patients. Moreover, new small-molecule circadian rhythm modulators identified by Kyeong et al. may point to new possible avenues for

designing targeted therapies to treat CVD (Kyeong et al., 2019). Understanding interactions of these molecules with circadian pathways in the cardiovascular tissues would open new possible avenues for treatment.

6.2.4. Individual variability and personalized medicine

Indeed, such studies as that of Zhang et al. who recently interrogated the function of circadian disruption and pharmacologic intervention in the model on circadian blood pressure rhythms, suggest a potential future where study areas characterize the genetic and phenotypic factors responsible for altered circadian rhythm presentation. It is possible to expand the kind of research into genetics regarding polymorphisms associated with cardiovascular risk that influence circadian regulation (Zhang et al., 2021). It will be very important in designing individualized treatment plans that account for the specific circadian profile of a patient.

6.2.5. Integration of Multidisciplinary Approaches

Future studies must therefore be multidisciplinary and find insights in both chronobiology, cardiology, nutrition, and behavioral science to further establish these interactions and circadian rhythm relationship with lifestyle factors and cardiovascular health. Such cooperative studies can explain the role of sleep, diet, and exercise on circadian rhythms and may develop practical insight into a more holistic approach in preventing and managing CVD.

7. Conclusion

Circadian rhythms are increasingly recognized to take part in a critical role in the regulation of cardiovascular health. They can influence virtually all variables that contribute to the control of blood pressure, vascular function, and metabolic homeostasis. The increased danger for hypertension, atherosclerosis, and other cardiovascular diseases associated with disruptions in these rhythms-of often modern lifestyle origin-underscores the clinical importance of circadian pathophysiology. The critical pathways involve circadian cardiovascular pathophysiology through autonomic imbalance, oxidative stress, and inflammatory responses. Lifestyle modification and pharmacological agents targeting circadian pathways, besides chronotherapy, would form part of therapeutic interventions for overcoming the risk induced. Systems biology approaches may provide a comprehensive framework to analyze complex interactions of circadian rhythms and cardiovascular health on the molecular, cellular, and systemic level. Future research should therefore pay more attention to filling up some of these existing knowledge gaps to develop individually specific interventions for enhancing circadian functionality. Taking an interdisciplinary approach by healthcare professionals and practitioners could eventually help patients alleviate circadian misalignment in favor of an optimization of better clinical outcomes as the prevalence of cardiovascular diseases drops in the world's population. This proactive alignment of circadian health with therapeutic interventions could transform the approach to preventing and managing cardiovascular disease globally.

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Author contributions

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