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The Influence of Circadian Rhythm on Cardiovascular Diseases

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Abstract: Cardiovascular and cerebrovascular diseases are common acute clinical conditions characterized by sudden onset, rapid progression, high rates of disability and mortality, and poor prognosis, often posing life-threatening risks. Ischemic heart disease and stroke rank as the first and second leading causes of death worldwide, respectively. The circadian rhythm, governed by a hierarchical system of central and peripheral oscillators, regulates biological activities in a time-dependent manner. The dominant central pacemaker, located in the suprachiasmatic nucleus of the hypothalamus, synchronizes with geophysical time through light signals. Peripheral tissues, in turn, are influenced by this master pacemaker via neuronal and humoral signals, which coordinate circadian physiology and behavior. Cardiovascular physiology exhibits distinct circadian rhythms, with parameters such as body temperature and blood pressure showing significant diurnal variations. Coagulation function, blood pressure, vascular function, endothelial health, and lipid metabolism all exhibit significant diurnal rhythms. Studies have indicated that individuals engaged in shift work are more susceptible to abnormalities in vascular physiological factors, and atherosclerosis has been clearly associated with circadian rhythm disruption. Understanding the circadian mechanisms of the vascular system may represent an important avenue for preventing and treating cardiovascular disorders. By leveraging these rhythms, clinicians can optimize drug administration timing (e.g., chronotherapy with aspirin) to further reduce cardiovascular event rates and improve therapeutic outcomes. This article not only clarifies the circadian physiological patterns of the vascular system but also elucidates the correlation between vascular physiological abnormalities and shift work, as well as the potential risks of circadian disruption in the development of atherosclerosis.

Keywords: Cardiovascular diseases, Circadian rhythm disruption, Vascular physiology

1. Introduction

Cardiovascular and cerebrovascular diseases are common clinical conditions. They are characterized by sudden onset, rapid progression, high disability and mortality rates, poor prognosis, and complex conditions that often endanger patients' lives. According to reports from the World Stroke Organization (WSO), the second leading cause of death worldwide is still stroke. The number of stroke patients is large and growing rapidly, especially among young people and in low- and middle-income countries (LMICs), where nearly 90% of the global stroke burden is concentrated [1]. This situation urgently calls for measures to reduce the incidence of strokes. Circadian rhythms are endogenous rhythms lasting roughly 24 hours (24 ± 4 hours). They are widely distributed and regulate

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most (if not all) of the major physiological systems in mammals. The physiology and behavior of animals both exhibit circadian periodic changes, such as the sleep-wake cycle, as well as physiological processes including the nervous system, metabolism, endocrine system, cardiovascular system, and immune system. Mammalian circadian physiology is built on a hierarchical network of oscillators, both central and peripheral. The master central heartbeat is located within the suprachiasmatic nucleus (SCN) in the hypothalamus. Diffusible SCN signals are sufficient to regulate receptor circadian rhythms. Peripheral clocks respond to phase-adjusting signals from the SCN; this is crucial for maintaining the optimal phase connection between the central and peripheral oscillators. Direct SCN output channels include efferent connections to other brain areas (mostly the hypothalamus) as well as humoral signals such as glucocorticoid and melatonin oscillations. This route is vital for sustaining the numerous periodic changes in the neurological, metabolic, endocrine, and cardiovascular systems that are critical to human health [2]. Moreover, studies have demonstrated a close relationship between circadian rhythms and cerebrovascular physiology. Blood pressure and body temperature exhibit significant circadian variations. The combination of a relative decrease in both systolic and diastolic blood pressure during sleep is the strongest determinant of the risk of vascular damage in the systemic circulation and vital organs, as well as the risk of morbid and fatal cardiovascular disease (CVD) events. In most studies conducted to date, shift work and night shifts have been shown to harm workers' health. Many health problems have been identified, such as increased incidence of cancer, sleep disorders, gastrointestinal problems, neuropsychiatric issues, and cardiovascular damage. These effects are believed to be associated with the desynchronization between the day-night cycle and the internal biological clock [3]. In this review, we summarized the circadian variations in various aspects of vascular physiology and discussed the optimization of medication timing based on circadian rhythms to enhance therapeutic efficacy. Additionally, we explored the alterations in normal vascular physiological factors under circadian disruption, using shift work as an example, and analyzed the correlation between circadian disruption and atherosclerosis.

2. Mechanisms of circadian rhythm regulation

Mammals possess a highly complex circadian rhythm system, with the central pacemaker being the suprachiasmatic nucleus (SCN) in the brain and peripheral clocks present in virtually all body cells. Light signals are perceived by the retina and transmitted to the central clock to achieve synchronization with geophysical time, which are transmitted to SCN neurons via electrical signals. The circadian physiology and behavior are regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus through the synchronization of neuronal and humoral signals. The SCN acts as a bridge between the external environment and the body's internal physiology. It can directly control these organs through neural pathways or transmit circadian information via hormones, thereby influencing the circadian physiology of peripheral organs in mammals, including humans [4]. As a result, renal activity, the endocrine system, the cardiovascular system, brain activity, metabolism, the immune system, and physical fitness all exhibit stable and well-coordinated circadian fluctuations. Moreover, these rhythms continue to persist even in constant conditions, where the organism receives no external time cues, suggesting they are regulated by an endogenous circadian timing system [5]. The molecular foundation of the peripheral vascular clock is comparable to that of the central clock because they both rely on the same transcriptional regulators: Bmal1 and Clock (Circadian Locomotor Output Cycles Kaput). Target genes like Period (Per1, Per2, Per3), Cryptochromes (Cry1, Cry2), Rev-erbα (NR1D1), and Dec1/Dec2 have E-box cis-regulatory enhancer sequences in their promoter regions that their protein products bind to in heterodimers. This connection promotes gene transcription, generating a system of three negative feedback loops and one positive feedback loop that regulates Bmal1 transcription and the heterodimerization of Bmal1 and Clock proteins, eventually preserving

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circadian rhythmicity. Additionally, the hypothalamus can secrete hormones that influence the sensitivity of target endocrine organs to pituitary signals through its effects on the autonomic nervous system (ANS). Thus, the hypothalamus can selectively target a group of organs through the ANS, altering their blood supply and responsiveness to specific hormones [6]. Currently, there are no studies on the hypothalamus influencing cardiac circadian rhythm through the ANS. However, research using cultured mouse cardiomyocytes has demonstrated that these cells are not affected by neurohumoral factors and has shown that serum alters circadian clock gene oscillations in adult rat cardiomyocytes, with norepinephrine controlling the circadian clock in these cells [7].

3. Circadian regulation of cardiovascular physiology

3.1. Diurnal blood pressure fluctuations

Despite being influenced by various factors such as emotions, ambient temperature, and endocrine factors, blood pressure (BP) exhibits distinct diurnal patterns in most individuals. BP gradually rises during the late sleep period, rapidly increases upon waking and initiating daytime activities, and shows two daytime peaks—a morning one and an afternoon/evening one. There is a smaller nadir during midday. During nighttime sleep, systolic BP decreases by 10-20%, while diastolic BP decreases slightly less compared to the average during wakefulness [8]. Both BP and heart rate display clear and predictable circadian rhythms. In adults, systolic and diastolic BP may vary by up to 50 mmHg within 24 hours, and heart rate may fluctuate by up to 25 beats per minute. The product of systolic BP and heart rate (DP) shows two secondary peaks approximately 3 and 13 hours after awakening. The nadir of the DP circadian rhythm occurs during sleep, around 3 hours before waking in the morning [9].

3.2. Vascular function and endothelial health

Endothelium is the primary system regulating vascular smooth muscle contraction. Endothelial cells generate redox-active chemicals, which are important signaling molecules for the dilatation and contraction of neighboring vascular smooth muscle cells. Endothelial cells produce redox-active compounds that act as signaling molecules, causing surrounding vascular smooth muscle cells to dilate and contract. Under the action of endothelial nitric oxide synthase (eNOS), nitric oxide (NO) is generated from L-arginine; hydrogen peroxide (H_2O_2) and superoxide are produced by NADPH oxidase (Nox); meanwhile, superoxide is generated by cyclooxygenase-1 (COX-1); and epoxyeicosatrienoic acids (EETs) are synthesized by cytochrome P450 (Cyp450) through its activity. In the vascular system, Nox and eNOS exhibit circadian rhythms. Increased sympathetic activity can cause vasoconstriction, but the peak of eNOS signaling can prevent this from happening. During the active phase, overall peripheral resistance increases are kept to a minimum. In addition, increasing sympathetic activity reduces heart contractility; excessive increases in blood pressure are effectively prevented [10]. During the active phase, vascular smooth muscle cells may relax due to increased amounts of H_2O_2 from various sources (eNOS, Nox-1,4, and mitochondria). This helps to counterbalance the effects of nitric oxide signaling on total peripheral resistance and blood pressure during the active period. However, endothelial function in the aorta of Bmal1 mutant animals is compromised [11].

3.3. Coagulation and cardiovascular risk

Research has shown that heart attacks, sudden cardiac deaths, and unnoticed heart problems happen more often in the morning [12]. The circadian rhythm of coagulation function may have a direct correlation with this phenomenon. Different signs of platelet activation are highest around 9 a.m.,

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including activated αIIbβ3, platelet factor 4 (PF4), β-thromboglobulin (β-TG), glycoprotein Ib (GPIb), and P-selectin. This evidence shows that the early morning peak of unfavorable cardiovascular events observed in epidemiological research could be attributed to endogenous circadian modulation of platelet activity [13]. Platelets are a key factor in arterial thrombosis. Therefore, aspirin is the cornerstone of secondary prevention because it inhibits platelet function. The diurnal variation in coagulation and fibrinolysis activity shows increased coagulation activity and decreased fibrinolysis activity in the morning, which may increase the risk of thrombosis. Multiple studies have found that taking aspirin in low doses at night is more effective at inhibiting morning platelet activity than taking it in the morning. Taking aspirin at night may reduce the proportion of uninhibited platelets in the morning (from 10% to 5%), thereby lowering the risk of cardiovascular events [14].

3.4. Lipid metabolism and cardiovascular risk factors

Dyslipidemia is largely defined by a decreased concentration of serum high-density lipoprotein cholesterol (HDL-C) or raised blood levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and serum total cholesterol (TC). A diet high in fat and calories can lead to dyslipidemia, which in turn can cause endothelial dysfunction. Therefore, dyslipidemia is a well-established risk factor for cardiovascular disease (CVD). Concurrently, components of the circulating lipid profile, particularly modified low-density lipoprotein cholesterol (LDL-C), may precipitate within the intima of the arterial wall and play a role in subsequent atherosclerosis. [15].

In this part, we look at the relationship between circadian rhythms and cholesterol production and absorption. Endogenous cholesterol synthesis and intestines taking in dietary and biliary cholesterol interact to maintain cholesterol homeostasis, which is an important driver of metabolic health. Plasma indicators show the metabolism of cholesterol, including synthesizing (desmosterol, lathosterol, mevalonic acid, squalene), gastrointestinal intake (campesterol, stigmasterol, cholesterol), and liver acid creation (7α-hydroxy-4-cholesten-3-one [C4]) including healthy and ill people. The enhancement of cholesterol absorption is caused by an increase in dietary cholesterol intake, and this effect can be offset by a reduction in endogenous cholesterol production. The circadian rhythm is evident in both cholesterol and bile acid synthesis, with interactions between the two processes. Multiple studies have demonstrated that cholesterol levels peak at night [16]. Another study examined the combined effects of light and non-light stimuli on liver function and clinical plasma lipid markers—including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, albumin, globulin, and total protein—revealing an overall pattern of elevated levels at night [17].

Disruption of clock genes can cause dyslipidemia. The transcription levels of clock genes and adipokines (such as adiponectin, resistin, and visfatin) all follow circadian cycles. Obesity slightly lowers the constant expression of these genes. The CLOCK gene is expressed in both subcutaneous and visceral adipose tissues, and visceral obesity-related cardiovascular risk emphasizes its potential significance in metabolic diseases. Circadian rhythm also influences the transcript sequence within human adipose tissue, including circadian regulation affecting about 25% of transcribed genes. Genes related to PER1-induced oscillations have been identified as additional regulatory sites in obesity. The transcription levels of CLOCK genes and adipokines all follow a 24-hour cycle. Obesity reduces the expressive rhythm of these genes. The reduction of BMAL1 expression causes a dramatic decrease in lipogenesis and the expression of numerous important lipogenic/adaptogenic proteins. In contrast, overexpression of BMAL1 in adipocytes promotes lipid production. Several important lipid metabolism regulators and enzymes involved in triglyceride metabolism retain their circadian rhythmic expression in clock-disrupted animals [18].

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4. Disruptions in circadian rhythms and cardiovascular diseases

4.1. Shift work and cardiovascular risk

Shift work is a common work arrangement in which employees follow a rotating schedule to ensure continuous operation of enterprises or institutions. However, working against the circadian rhythm for extended periods can disrupt these circadian rhythms and impact health. This study examines the association between shift employment and cardiovascular risk variables during the last decade. Over the last decade, research has focused on the possible elevated risk of hypertension among shift workers, with the period of exposure likely impacting this connection. Triglyceride levels were observed to be considerably higher while working shifts. However, there was no apparent link found between shift work and total cholesterol, HDL-C, or LDL-C. Furthermore, studies on endothelial dysfunction found that shift workers had much higher triglyceride level and insulin resistance. Shift work has been shown to have negative consequences on workers' cardiovascular health [19].

4.2. Atherosclerosis

Atherosclerosis is the leading cause of myocardial infarctions, stroke, and cardiovascular diseases. Dyslipidemia, hypertension, obesity, smoking, and diabetes are significant risk factors for atherosclerosis. The gradual buildup of fibrous and fatty components in big arteries leads to the development of atherosclerosis. Circadian disruption may also play a role in atherosclerosis, according to growing evidence. Normal diurnal blood pressure variation is crucial for cardiovascular health. In clinical practice, cardiovascular events and thromboembolic occurrences exhibit distinct diurnal variations, with a higher incidence in the morning-to-noon period. Circadian disturbance has a substantial influence on vascular physiology. Circadian rhythms can impact the pathophysiology of atherosclerosis by controlling inflammatory processes and metabolism. Furthermore, circadian disturbance can impair endothelial function, namely endothelial nitric oxide synthase (eNOS) expression and NO generation, both of which are linked to the prevalence of cardiovascular disease. Under normal circumstances, during the light period, the reduced generation of NO in the morning leads to a decrease in endothelial-dependent dilatation. Reduced production of nitric oxide (NO) may lead to the increased incidence of cardiovascular diseases in the early morning. At the same time, circadian rhythm abnormalities may promote the recruitment of white blood cells to the injured endothelium. This accelerates the development of atherosclerosis. Inflammatory responses of monocytes and macrophages are key factors in the formation of atherosclerosis. When blood cholesterol levels are elevated, inflammatory Ly6chi monocytes attach to the irritated endothelium and eventually become lesion macrophages, which are important stages in the onset and exacerbation of atherosclerosis. The balance of coagulation and fibrinolysis is also influenced by circadian rhythms. Fibrinolytic activity is at its lowest level during the night and gradually increases before dawn. Platelet counts peak in the afternoon, but they are most active in the morning. Thromboembolic events occur more frequently in the early hours of the day [20].

5. Conclusion

Cardiovascular disorders are a leading cause of mortality in humans, characterized by acute onset, rapid progression, and high rates of disability and mortality. Several investigations have discovered that the peripheral circadian clock in the vasculature is composed of similar key transcription genes (Clock and Bmal1) as the central circadian mechanism. Various vascular physiological factors exhibit distinct circadian rhythms. For instance, blood pressure becomes its lowest throughout the night. In endothelial cells, eNOS and Nox display 24-hour rhythmic oscillations within the vascular system. Disruption of clock genes can lead to dyslipidemia, with levels of total cholesterol, low-density

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lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, albumin, globulin, and total protein all showing a pattern of nocturnal elevation. Multiple indicators of platelet activation also exhibit pronounced temporal variations, peaking in the morning. The circadian rhythm plays a crucial role in cardiovascular health, with its disruption causing abnormalities in the vascular system. Shift work has been shown to have adverse effects on workers' cardiovascular health, including blood pressure, lipid profiles, and endothelial function. Atherosclerosis is more likely to happen when these irregular vascular factors are present because of the disruption of circadian rhythms, which is detrimental for vascular health. Future research should further explore the specific mechanisms underlying the relationship between circadian rhythms and cardiovascular diseases and develop treatment strategies based on circadian regulation, such as adjusting medication timing, to achieve better therapeutic effects.

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