

# Circadian Rhythms: Attributes, Disruption, and Implementation in Cardiometabolic Health

<sup>1</sup>Narsingh Verma, <sup>2</sup>Shipra Bharadwaj

## ABSTRACT

It is a well-known fact, proved by evidence, that all the organisms consist of an internal biological clock, right from the single-celled organisms to humans. In the hierarchy of classification of vertebrate, these rhythms have shown to play an important role concerning the physiological aspects of all organisms. Not only are these rhythms related to sleep, seasonal migration, reproduction, etc., in animals, but also, in humans, circadian rhythms control various vegetative functions including regulation of temperature, cardiac activity, endocrine secretion, blood pressure (BP), oxygen utilization, metabolic rate, menstrual and ovarian cycles, and other body functions. The change in the normal pattern of the circadian clock because of genetic, behavioral, and various environmental factors can produce cardiovascular, metabolic, and endocrinal disorders including hypertension and diabetes. The concentration of glucose in plasma displays circadian variation; in the morning hours, it is the highest. Since the level of insulin depends on the feeding behavior, the glucose concentration follows the daily rhythm of intake of food. On the contrary, BP and other cardiovascular reflexes have characteristic and diurnal circadian rhythms. Circadian trends are exhibited in many cardiovascular pathophysiological conditions like stroke, myocardial infarction, rhythm disorders, and bed death syndrome. There is enough evidence to show that disruption of circadian rhythms can act as a risk factor for the development of cardiovascular diseases. Recent research also suggests that the circadian clock and associated central as well as peripheral genes are responsible for glucose and lipid metabolic rhythms.

**Keywords:** Cardiometabolic functions, Chronomics, Circadian rhythms, Midline estimating statistic of rhythm.

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## INTRODUCTION

Biological functions are precisely organized in time in the form of circadian rhythms. These rhythms are an

integral part of the vegetative systemic functions, displaying endogenous oscillations from seconds, minutes, and hours, days, weeks, and even months and years. These rhythms are present in almost every cell including those of plants, bacteria, animals; isolated cultures of the cells of animals, plants, bacteria, and even cultured cells possess these rhythms. The suprachiasmatic nucleus (SCN) acts as a master circadian pacemaker. The SCN is synchronized by environmental light-dark cycles via photoreceptors and neural pathways. These diurnal oscillations are regulated by clock genes expressed in the SCN and other cells. The SCN acts as a central pacemaker and entrains the lower circadian clock by various neuroendocrine pathways.<sup>1</sup> It also serves as a central clock, while the peripheral organs have a peripheral clock.<sup>2</sup> The light input from the retina is received by the SCN and then converted to neural or hormonal signals, which generate biological rhythms.<sup>3</sup> In humans, the core clock genes are constituted by *Bmal1* (brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1), *CLOCK* (circadian locomotor output cycles kaput), *Per* (Period), and *Cry* (Cryptochrome). These genes generate a system for feedback and regulation.<sup>4</sup> These clock genes, in turn, control target genes and also regulate circadian rhythms of various biochemical and physiological processes.<sup>4</sup> The coordination of all these systemic genes is necessary for optimal physiologic functions and maintenance of mental and physical health.<sup>5</sup> The loss of normal synchronization between and among central and peripheral oscillations leads to various diseased conditions. Circadian disruption at the systemic and molecular levels is linked to sleep disorders, cardiovascular and metabolic diseases, cancer, and psychiatric disorders. In addition, some new data suggest that disruption of circadian rhythms may result in pancreatic clock disruption, leading to diabetes and obesity.<sup>6-8</sup>

## Circadian Rhythms of the Cardiovascular System

Various physiological vegetative functions like BP, heart rate, cardiac contractility, vascular reactivity, and various homeostatic factors follow a characteristic circadian pattern. There are many studies suggesting that the onset of various cardiac disorders exhibits a circadian pattern and the best examples can be acute coronary syndrome or atrial fibrillation, which is more common in morning hours. Some other published reports by our group suggest

<sup>1</sup>Professor, <sup>2</sup>Research Scientist

<sup>1</sup>Department of Physiology, King George Medical University Lucknow, Uttar Pradesh, India

<sup>2</sup>Department of Medicine, King George Medical University Lucknow, Uttar Pradesh, India

**Corresponding Author:** Narsingh Verma, Professor, Department of Physiology, King George Medical University, Lucknow, Uttar Pradesh, India, e-mail: narsinghverma@gmail.com

that several cardiac functions show 24-hour and 7-day *circaseptan* and circadian variation, including rate of heart and arterial pressure (BP).<sup>9,10</sup> The cardiovascular system and BP have a definite and reproducible pattern exhibited by daytime elevation and nocturnal decline.<sup>11,12</sup> Various parameters of the cardiovascular system, like BP and heart rate, keep on changing across the 24 hours, which is in synchrony with the rest–activity cycle.<sup>13,14</sup> This diurnal BP variation is modulated by internal factors, such as gender, race, tone of autonomic nervous system, vascular hormones, and other blood, plasma, and renal variables.<sup>15,16</sup>

The various factors determining arterial pressure show circadian variability like plasma and urinary mineralocorticoids, plasma cortisol and urinary markers like sodium, angiotensin II, plasma and urinary epinephrine, norepinephrine, and prostaglandins. Chronobiological analysis of BP for at least 7 days helps in diagnosing circadian hyper-amplitude-tension (CHAT), a condition in which excessive circadian BP amplitudes are seen even before the chronic established hypertension.<sup>17-19</sup> This CHAT is considered as a very high and independent risk factor for stroke. Our group has shown that the CHAT reversal is possible by changing the timing of administration of few drugs when more than one drug is being used. Based on rhythmic, fixed diurnal variations of BP, people have been grouped as dipper and nondipper broadly. Dippers are those subjects who have a nighttime (sleep period) fall in BP with respect to their daytime (wake period) value. In contrast, nondippers are those in whom there is no significant fall in BP during nighttime. The reproducible characteristic circadian pattern of data can be obtained by ambulatory BP monitoring (ABPM). The chief determinant of circadian pattern of BP appears to be the sympathetic reactivity. Serial measurements of plasma catecholamine over 24 hours indicate that both norepinephrine and epinephrine have a pattern of variability very similar to that of BP. The increased sympathetic activity during arousal from sleep may be an important factor in producing the sharp, rapid, early morning BP increases. Norepinephrine levels, in particular, appear to demonstrate a slight overshoot toward the end of morning-arousal process, similar to that seen with BP.<sup>20</sup> Early studies using intra-arterial ABPM devices established that 24-hour BP curves are reproducible when studied on consecutive days and separate weeks apart. Studies have demonstrated that various cardiac events like arrhythmias, sudden cardiac deaths, episodes of stable angina, unstable angina, acute myocardial infarction, and cerebrovascular events are predominant in the morning hours. The cause of early morning predominance of these adverse events is mainly attributed to early morning rise in BP.<sup>21</sup>

## Chronocardiology and Circadian Rhythm Disruptions

Circadian rhythms are disrupted during cardiovascular disease or it could be *vice versa*. Various changes in circadian rhythms can influence or even construct various diseases. The onset of various cardiac emergencies like myocardial events, sudden cardiac death, and cerebrovascular accident increases between 06:00 and 12:00 hours. The reason behind it mainly may be due to increased sympathetic activity after an individual gets out of bed, and also due to the interaction between catecholamines and platelets, thus affecting atherosclerotic plaque pathophysiology. These circadian clocks exist within cardiac myocytes and smooth cells of the vessels. These circadian variations have been seen exhibited by various circulatory reflexes, factors of platelet aggregation, coagulation factors, and the concentration of fibrinogen and fibrin-lysing system.<sup>22</sup> It is an established fact that the SCN receives external cues or zeitgebers like SCN nucleus processes external signals like ambient light and inputs from the brain for regulation of variety of physiological functions like body temperature, sleep/wake cycles, and secretion of hormones, such as cortisol, melatonin, thyroxin, and vasopressin,<sup>23</sup> which are regulated by SCN and possibly by melatonin (MT) receptors MT<sub>1</sub> & MT<sub>2</sub>, that have been reported in human coronary arteries. Animal studies suggest that depending upon the type of receptor being activated, melatonin can have an effect on vasculature. There is vasoconstriction with MT<sub>1</sub> and vasodilatation with MT<sub>2</sub> receptor activation. Endogenous production of melatonin is approximately 30 mg/day, but the peaks can go very high up to 100 pg/mL.<sup>24,25</sup>

Chronobiologic considerations, in turn, aim at chronological risk assessment using values that may lie well within the physiological range as a step toward prevention. In both physiological and pathological conditions, BP and heart rate follow the activity levels of the body and brain, especially during sleep and wakeful conditions. Nocturnal BP value and heart rate variations are according to sympathetic activity. The morning values of norepinephrine are mostly higher than night (sleep) values, but they may not be said to be highest values of the last 24 hours. This also suggests that, under some conditions, the morning incidences of myocardial infarction and/or other high cardiac death rates may be due to increased response of these organs to circulating norepinephrine levels.

The inherent variability of the rhythm in most of the healthy individuals has less amplitude. This genetically designed day–night difference is amplified by activity and stress profile; and, in majority of individuals, this trough-to-peak difference amounts to the tune of 15 to

25 mm Hg. Various systemic diseases do have the influence on expression and features of this circadian change. In primary and secondary hypertension, the midline estimating statistic of rhythm (MESOR) values (24-hour time adjusted mean) and amplitudes of the rhythm may be altered; in few cases, the rhythm itself may be obliterated. In secondary hypertension, nighttime values of BP may be increased and reverse dipping patterns may be seen, whereas many disease conditions have nocturnal BP deregulation. The nondipping pattern of circadian BP variability is clinically important as there is increase in cardiovascular morbidity.<sup>25</sup> Deregulated autonomic nervous system functions, syndrome Z (disturbed breathing due to sleep disorder), and other qualitative and quantitative sleep defects are known causes of altered circadian BP profile, while certain secondary causes of hypertension may enhance the rapidity of BP change. We do not know much about the pathophysiology of nocturnal rise in pressure, but the increasing age and ethnicity are important determinants.<sup>26</sup>

## IMPLICATIONS OF CHRONOTHERAPEUTICS FOR CARDIOVASCULAR DISEASES

A major objective of chronotherapy for cardiovascular diseases would be to ensure the appropriate drug delivery and the required concentrations according to circadian patterns of the disease. At present, there are not enough data to know whether altering the dosing time of a conventional drug can have any benefits. Few recent studies have evaluated the effect of timing of drug on circadian BP patterns, with somewhat inconsistent results.<sup>27-29</sup>

A study with angiotensin-converting enzyme inhibitors has shown that evening dosing of drug was able to reduce nocturnal pressure more effectively than morning doses.<sup>27</sup> The daytime BP in both groups did not have any significant difference. The increase in dipping may be dangerous in the elderly and high cardiovascular-risk individuals. In contrast to these studies with atenolol,<sup>30</sup> nifedipine GITS or amlodipine, showed no differential effects on BP. All these studies are not significant because of small sample sizes. The first therapy following chronomedicine concepts has been developed recently. This mode of therapy matches the circadian pattern of BP and myocardial ischemia. The calcium channel blocker drug, verapamil, has been employed in this delivery system that has a delay in release for approximately 4 to 5 hours after dosing and then has an extended release for approximately 18 hours. When taken at bedtime, the delivery system of this therapy provides optimal drug concentrations in the morning hours, the most dangerous period for all these events to occur. Now with the effects

on this system, the effect of drug is higher at the time of requirement. This delivery system has the maximum effect during the daytime and minimum effects during the nighttime when the requirement of the effect of drug is decreased because BP goes down during nighttime. This mode of drug delivery is novel, but we must not forget that all long-acting drugs do have almost the same effects. The effect of night dosing of drugs is very much formulation-dependent. For example, antihypertensive medications with conventional delivery systems can increase nighttime ischemic episodes when given to patients of "extreme dipping." Alternatively, doxazosin, which has a slow rate of absorption, does not excessively decrease night BPs when administered at bedtime, but the control of early morning peak is satisfactory. Recent studies have much evidence to suggest that antihypertensive and anti-anginal therapies can be developed, which can follow the circadian patterns. The implications of this type of therapy may be important since cardiovascular events occur more frequently in the early morning hours.<sup>31</sup> However, more outcome data are required to implement all such formulations.

## Assessing Circadian Variability of BP and Heart Rate: Ambulatory BP Measurements

Ambulatory BP and heart rate measurements have evolved as one of the crucial tools in assessing circadian variability of the cardiovascular system. In our previous studies on coronary artery disease and shift workers by employing the 7-day/24-hour ambulatory monitoring of BP and heart rate, it has been proven that timed analysis of ambulatory BP and heart rate using nondipping and dipping patterns, MESOR, double amplitude, acrophase, and hourly fractionated hyperbaric indices are important early predictive parameters of any cardiovascular morbidity and mortality. Implementing chronobiological analysis in routine clinical treatments can be helpful in diagnosis of BP variations, dipping status, excluding of white coat hypertension, taking decisions on treatment for elderly patients, identifying nocturnal changes in BP, resistant hypertension, determining the efficacy of drug treatment over 24 hours, and diagnosing and treating hypertension in pregnancy and hypotension.

## CHRONOMICS OF ALTERED METABOLIC STATE

In mammals and humans, feeding provides nutrients like glucose, amino acids, and lipids, which are essential for metabolism and act as fuel for the metabolic pathways. During the resting period, the stored energy and substrates are utilized to maintain metabolic homeostasis.<sup>32</sup> Glucose concentrations in blood are maintained within physiological limits by signaling mechanisms responsible



for secretion of insulin and glucagon. Plasma glucose concentrations do follow a characteristic circadian variation, with the highest levels in the morning and day (active) time. It is also influenced by food patterns of the individuals. On the contrary, autonomous circadian rhythms have been observed in pancreatic islet cells. Clock mutants, as well as *Bmal1* mutants, show decreased secretion of insulin due to defective size and function of islet cells, leading to impaired glucose tolerance. These disturbed clock mechanisms in the endocrine beta-cells will produce an impaired insulin release, which will ultimately produce hyperglycemia.<sup>33</sup> Recently, it has been found that mutations in clock genes of alpha cells may alter the glucagon secretion, which can compensate for decrease action of insulin.

The researchers show that beta-cells have their own dedicated clock, which regulates the outcome of the proteins and genes responsible for secretion of insulin. Any disturbance in these clock genes can produce diabetes.<sup>34,35</sup> These circadian and metabolic systems are interconnected at the genetic level.

### **CIRCADIAN DISRUPTION AND METABOLIC DISEASES**

There is plenty of evidence that suggests that circadian disruption is one the major cause of metabolic diseases. The disruption of these circadian patterns may influence the pathophysiological mechanisms involved in diabetes, inflammation, fibrinolysis, fluid balance, and cardiovascular diseases including hypertension. The direct linkage between circadian mechanism dysfunction and metabolic abnormalities is demonstrated by phenotypes of circadian-clock gene mutants, knockouts, or disruptions.

#### **Role of Diet and Lifestyle on Circadian Rhythms Disruption**

There are very interesting evidences that lifestyle and feeding habits have a strong impact on proper synchronization of circadian rhythms. The high-fat diet is instrumental in expression of circadian clock genes. In most cases, dietary factors determine the various aspects of chronomics of circadian clocks. However, more consistent data are needed to establish this fact. In one study, 6 weeks of high-fat diet was able to change gene expression as well as desynchronized behavioral and endocrine rhythms including the pancreas and liver.<sup>36</sup>

### **EFFECT OF LIGHT POLLUTION**

Light has a powerful influence on living organisms. The light stimulus reaches the retina and then the message reaches the SCN nucleus. The neurotransmitter involved is glutamate. The intensity and other variables of light

exposure may change the rhythmicity of the internal circadian clock. During darkness, sleep occurs and sleep is attributed to cell repair and other physiological processes like mental recovery. The neurotransmitter serotonin is responsible for mood state and dips at night, while melatonin induces sleep and is responsible for stimulation for deoxyribonucleic acid repair. Thus, these neuroendocrine rhythms, along with other physiological processes, are programmed to occur at specific moments of the circadian cycle. The disruptions in circadian rhythm can occur both in very low or bright light; the duration and periodicity of light is also important. Some other evidences indicate that artificial light of both low and high intensity are involved; thus, even the light intensities used for households and workplaces can have an impact on the biological clock and circadian rhythms. The consequence of a shifted clock is manifested with insufficient sleep and rest, melatonin deficit, and hormonal insufficiency.

### **IMPLEMENTATION OF METABOLIC CHRONOTHERAPEUTICS**

There are specific circadian rhythms for glucose and cholesterol synthesis, and it is influenced by both the sympathetic and parasympathetic inputs in glucose metabolism. Recently, we have observed enough evidence to suggest that restricted feeding can change rhythmic patterns of clock genes in the liver and thus, uncouple them from the central clock, which has not changed. About 350 circadian transcripts have been identified in the liver, 10% of which, including the core gene *Per2*, maintain rhythmicity in the absence of a functional hepatocyte clock responsible for behavioral, hormonal, and autonomic rhythms, in the regulation of liver Clock gene expression. Cholesterol synthesis takes place at higher paces during nighttime in comparison with daytime, and some of the individuals show reversed patterns with inverted diurnal cholesterol synthesis. Therefore, it is better to take statins (5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) in the evening rather than in the morning. Free cholesterol levels are reported to be the lowest from 2 to 6 PM and peak at 6 AM. Advanced diagnostic technologies based on circadian variations like ambulatory glucose monitor and ambulatory Glucose profile are of great advantage in determining glucose levels and rate of change of glucose, which serve as alerts and alarms for actual or impending hypo- and hyperglycemia.

### **CONCLUSION**

Recently, there has been a sharp rise in prevalence of cardiometabolic diseases. These diseases have a complicated genetic and environmental basal influence on pathophysiology. The disharmony between our intrinsic

and extrinsic clock creates an imbalance between energy intake and utilization via metabolism, creating a pathway for several cardiometabolic disease. Current evidence suggests that molecular central and peripheral clocks are important for regulation of metabolic and cardiovascular functions. Disrupting this process through mutations in the core clock genes or by interfering with the environmental zeitgebers that entrain the molecular clock may modulate the functions of the cell and tissue, with loss of the synchrony that normally exists between the environment and physiology. This leads to the development of cardiometabolic pathway abnormalities. Ultimately, a closer understanding of the roles of the central and peripheral molecular clocks in the pathogenesis of cardiometabolic disease may help to develop novel therapeutic approaches to combat obesity, type II diabetes, and associated cardiovascular disease. Disruption of the circadian clock, because of shift-work or bad sleeping habits and late night snacks can cause severe disturbances in these rhythms. There are a number of studies that describe the role of circadian clock genes and molecular regulating factors as discussed above mostly in animals; however, there is scarcity of similar data on humans, which is needed in future research to achieve insights into synchronization of environmental and internal clocks.

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