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Chapter

Myocardial Infarction and Circadian Rhythm

Ivana Škrlec, Svjetlana Marić and Aleksandar Včev

Abstract

Human physiological activity and condition during illness are under the control of the circadian rhythm. Circadian rhythms handle a wide diversity of physiological and metabolic functions, and the interruption of these rhythms has been linked to obesity, sleep disorders, metabolic and psychological disorders, and cardiovascular events such as myocardial infarction (MI), stroke, and vascular death. Disruption of circadian rhythms increases the risk of developing myocardial infarction, indicating that circadian genes might play an essential role in determining disease susceptibility. It is well known that many cardiovascular processes show daily variations depending on the circadian rhythm (blood pressure, heart rate), and the gene expression of the cardiomyocyte circadian clock influences myocardial contractile function, metabolism, and other gene expressions. We present a review of the latest knowledge on the impact of circadian rhythm and circadian rhythm genes on myocardial infarction. Today, in a time of personalized medicine, it is essential to know each person’s circadian rhythm for its treatment and possible inclusion in the diagnostic procedures.

Keywords: cardiomyocytes, circadian rhythm, myocardial infarction

1. Introduction

Everyday life is organized according to three different clocks: the solar clock which gives us light and temperature during the day, the social clock which determines the working day, and the biological clock which we notice during shift work or when we adjust to a reduced amount of daylight. In real life, the circadian clock is synchronized within 24 hours of the solar clock [1, 2].

It is known that almost all cardiovascular events occur in a circadian manner with a higher frequency in the morning after waking [3]. In the peripheral clocks of the cardiovascular tissues or cells, there is daily expression of the clock-controlled genes (CCG) synchronized and regulated by central clock [4, 5]. Disturbances of circadian rhythm can lead to cardiovascular disease.

Today we are facing a global epidemic of cardiovascular disease. In 2015 cardiovascular disease was the cause of 17.7 million deaths worldwide or 31% of total mortality. Of these 7.4 million deaths were caused by ischemic heart disease and 6.7 million by cerebrovascular diseases, according to World Health Organization (WHO) [6].
2. Circadian rhythm

Circadian rhythm is controlled by a molecular clock located in almost every cell. A hierarchical system organizes molecular clocks—the master clock is located in the suprachiasmatic nucleus (SCN) in the hypothalamus [2, 7], while the peripheral clocks are located in each organ or cell. The central clock regulates physiological functions via the autonomic nervous system, humoral mediators, and other still unknown factors [7, 8]. In the maintenance and generation of circadian or biological rhythm in humans, a whole series of anatomical (suprachiasmatic nucleus), neurological (retinohypothalamic paths) and neuroendocrine (melatonin) systems are involved, indicating that the biology of the circadian rhythm of humans is similar to that of animals [9].

The master clock in the SCN consists of about 100,000 neurons in humans. It is the only molecular clock that receives light as an input signal from the retina. Internal clocks are synchronized with light depending on the time of day. SCN receives a direct light signal from the retina via the optic nerve from the photoreceptor called the intrinsically photoreceptive retinal ganglion cell (ipRGC), which expresses the circadian photopigment, melanopsin [10]. The signal is further transmitted to peripheral clocks via the endocrine system [11, 12]. The central clock synchronizes each of the peripheral clocks in the body, and the primary circadian hormone is melatonin [13]. The pineal gland secretes melatonin during the night. Melatonin plays an essential role in maintaining the circadian rhythm depending on the period of light or darkness. The main difference between the master and peripheral clocks is in their degree of intercellular interaction. Peripheral clocks are under the influence of the master clock from the SCN via hormones, chemical signals and other metabolites (such as food), as well as by changes in the body, such as body temperature [11, 12].

On the other hand, due to the high degree of neuron connection the master clock in the SCN is not under the influence of internal signals but only under the influence of light [14]. Peripheral tissues integrate central clock signals with environmental factors (including sleepiness, physical activity, and feeding) and their autonomic rhythms which regulate the metabolism in a circadian manner [10]. The rhythm of the peripheral clocks in humans is measured by direct measurement of physiological changes, or by determining the expression of the clock genes. Central and peripheral clocks together control the daily circadian rhythm of the metabolism [15].

Feeding time is one of the key triggers or external factors that sets the phases of the peripheral clocks [15]. Complex feedback loops connect the circadian clock with metabolic pathways and integrate these systems independently of light [10]. It is believed that the central clock regulates the metabolism by hormones (primarily cortisol and melatonin) and synaptic signaling (via the autonomic nervous system) [10]. Feeding is a circadian event that serves not only as the output of the central clock, but also as an input signal for peripheral clocks because peripheral tissues communicate with the brain through ghrelin, leptin, glucose, and insulin. Circadian feeding contributes to the interworking of the clock and metabolism, which is crucial for metabolic homeostasis [16]. The central clock rhythm is primarily related to light, whereas peripheral tissue rhythms derive from the input of signals from the central clock, external factors (light, physical activity, feeding, and sleepiness) and the availability of numerous metabolites [15]. All these signals affect the molecular clock, creating a complex correlation between the circadian clock and physiological processes [10]. SCN coordinates all cellular circadian clocks in the organs and tissues through its rhythmic outcomes, to adapt physiology to Earth’s rotation [17].
The two clock systems become desynchronized when their drivers or stimuli do not coincide because different stimuli affect the phases of the central and peripheral clocks. This mismatch disrupts the metabolism because the two clock systems coordinate interlinked metabolic pathways. Circadian rhythm mismatch increases the risk of developing metabolic diseases [15].

The central clock is primarily triggered by light, and its rhythm is often measured by determining the concentrations of melatonin, cortisol or body temperature [15]. The expression of the clock genes is disrupted in pathological conditions. Such a change may result in different tissue response to external signals and accelerate tissue damage. The loss of synchronization can lead to various diseases, including an increased incidence of cardiovascular disease [18].

3. Molecular basis of circadian rhythm

The central clock genes are expressed in a circadian manner in the SCN, and light is one of the main initiators (so-called zeitgeber) and can reset the phase of the rhythm. The first circadian rhythm gene discovered was the Per gene in the fruit fly in 1971 [19, 20], while the first circadian rhythm gene discovered in the vertebrae was the CLOCK gene [21]. There are about 10 circadian rhythm genes known to regulate cyclic expression of mRNA and protein, via transcription and translation feedback loops [22]. In the SCN there are four essential proteins: ARNTL (Aryl Hydrocarbon Receptor Nuclear Translocator-Like) and CLOCK (Circadian Locomotor Output Cycles Caps) are activators, while PER (Period) and CRY (Cryptochrome) are transcription inhibitors. The feedback of the circadian rhythm gene maintains circadian oscillations in one cell at the transcriptional and posttranscriptional levels, and the transition from light to dark triggers these oscillations. The whole process of activation and repression of gene expression within the loop lasts for about 24 hours. These transcriptional factors trigger numerous physiological changes by acting on the expression of the same genes, and other clock-controlled genes [23, 24].

ARNTL and CLOCK heterodimers bind to regulatory elements of the promoters and enhancers (E-box) of the PER and CRY genes and stimulate their expression and the expression of other clock-controlled genes. Overnight the amount of PER and CRY proteins gradually increases, and heterodimers are created in the cytoplasm. The phosphorylated PER-CRY heterodimers are translocated into the nucleus where they inhibit the ARNTL-CLOCK protein complex. Therefore, during the day, transcription of PER and CRY genes is reduced, while the levels of PER and CRY protein decrease due to their degradation by ubiquitin. The PER-CRY heterodimers directly bind to the ARNTL-CLOCK complex, and as PER2 contains histone deacetylase, the chromatin structure changes, resulting in transcription termination. Also, the PER-CRY heterodimer is in interaction with RNA-binding proteins and helicase that are important in stopping transcription independently of the interaction with the ARNTL-CLOCK complex. Additionally, PER-CRY heterodimers regulate the transcription of various nucleic hormone receptors [25–28].

During the day a new cycle begins by the termination of the ARNTL-CLOCK heterodimer inhibition. Casein kinase 1 (CK1) controls the amount of phosphorylation or degradation of PER-CRY heterodimers and thereby determines the amount of PER-CRY heterodimer entering the nucleus and inhibiting the ARNTL-CLOCK complex. CK1 phosphorylates the proteins and thus regulates their activity [29].

The additional negative loop is REV-ERBα that binds to the REV-ERB/ROR response element (RRE) of the ARNTL and CLOCK genes, and prevents their transcription. Also, RORα (Retinoic Acid Receptor-related Orphan Receptor) binds
to the same regulatory elements of the ARNTL gene as well as REV-ERBα. With REV-ERBα degradation overnight, RORα promotes transcription of the ARNTL gene [30]. The second regulatory loop consists of ARNTL-CLOCK heterodimers which promote the transcription of the nuclear receptors REV-ERBα and RORα [31] (Figure 1).

Circadian clock genes have an essential role in many physiological processes. Thus, animal models demonstrate that the ARNTL gene plays an essential role in lipid metabolism because it induces the expression of genes involved in lipogenesis in adipose tissue in a circadian manner [32]. Pancreatic beta cells have a circadian clock dependent on ARNTL and CLOCK protein oscillations, which regulate insulin secretion depending on the stage of alertness. Abnormalities of the pancreas clock may trigger the onset of diabetes [33]. It was found that CLOCK polymorphisms are associated with body weight, the risk for metabolic syndrome and insomnia in humans [9, 32], and polymorphisms of the PER2 and PER3 genes are associated with sleep disorders [34, 35]. Some variants of CRY1 and CRY2 are associated with metabolic syndrome, particularly hypertension and increased triglyceride levels in the blood [36]. Many variants of the circadian rhythm genes are associated with the risk factors for the development of cardiovascular diseases such as blood pressure, glucose concentration [23, 37]. An overview of the essential circadian rhythm genes with their roles is shown in Table 1 [38, 39].

**Figure 1.** The molecular mechanism of circadian rhythm in humans. ARNTL and CLOCK activate transcription of CRY and PER, nuclear receptors (REV-ERBα and RORα) and other clock-controlled genes. CRY and PER heterodimerize and phosphorylate by casein kinases and translate into the nucleus where they prevent binding of the ARNTL-CLOCK to the regulatory regions of target genes. In the second feedback loop, REV-ERBα prevents the transcription of ARNTL because it binds to the RRE element, while overnight the same regulatory elements bind RORα and activate transcription of ARNTL. Also, ARNT-CLOCK heterodimers activate transcription of the REV-ERBα and RORα proteins. ARNTL—aryl hydrocarbon receptor nuclear translocator-like, CLOCK—circadian locomotor output cycles kaput, CRY—cryptochrome, PER—period, P—phosphate, RORα—retinoic-related orphan receptor alpha, RRE element—REV-ERB/ROR response element, Ub—ubiquitin.
Numerous studies on animal models, as well as human populations, have confirmed the association of the circadian clock gene with metabolic syndrome and cardiovascular diseases [15, 40, 41].

4. Cardiovascular diseases

The WHO data for 2017 show that cardiovascular diseases were the cause of 19.9 million deaths worldwide, and about 80% of deaths from cardiovascular diseases were due to myocardial infarction and stroke [42]. It is estimated that by 2030, 23.6 million people will die annually due to cardiovascular diseases [43].

Cardiovascular diseases are the primary cause of death in developed countries of the world, and in less developed parts of the world, this mortality is rising and overtaking mortality rates for infectious diseases [44].

There are variable and constant risk factors for cardiovascular disease. The variable risk factors are those that can be affected by therapy and lifestyle change, such as smoking, hyperlipoproteinemia, hypertension, and to some extent diabetes and homocysteinemia. The constant risk factors cannot be affected, namely age, genetic predisposition, gender, and menopause. The general risk factors which can be altered most are smoking, hypertension and hyperlipidemia, and obesity and diabetes whose prevalence has risen in the last few decades. However, some recent risk factors (fibrinogen, lipoprotein (a), homocysteine) should not be ignored. All of these contribute to total cardiovascular risk [45].

Cardiometabolic risk factors are determined by a cluster of metabolic and cardiovascular changes. Diabetes and obesity are also associated with reduced quality of life and increased economic burden on the person and society [46, 47]. Cardiovascular diseases and type 2 diabetes share common pathophysiological
mechanisms of insulin resistance and risk factors for cardiovascular diseases, such as metabolic syndrome. Excessive weight plays a significant role because fatty tissue becomes an active endocrine organ that secretes low-level inflammation mediators, and these stimulate the development of metabolic syndrome and vascular diseases [32, 48, 49].

5. Myocardial infarction

Myocardial infarction is the leading cause of mortality in developed countries and developing countries. It can be caused and triggered by different pathophysiological processes. Myocardial infarction is an inflammatory disease due to the death of myocardial cells because of complete coronary circulation interruption, which is in most cases a consequence of thrombotic occlusion of the coronary artery at the site of the activated atherosclerotic plaque. An electrocardiogram (ECG) of the ST elevation is only an indirect indicator of the fact that ischemia affects all three layers of cardiac muscle (endocardium, myocardium, and epicardium) [50].

ST-elevation myocardial infarction (STEMI) is the most severe form of acute coronary syndrome. Myocardial infarction is accompanied by increased cellular oxidative stress in the pericardial cavity [51]. The primary cause of infarction is platelet aggregation in the coronary artery. The platelet activity is the highest in the morning. Also, in the morning hours, mental and physical activity increase due to cortisol and catecholamine elevation, which increases cardiac output [45]. The biochemical markers of myocardial damage are cardiac troponin T or troponin I in serum. These biochemical markers are more reliable than those previously used, such as measurement of creatine kinase (CK). The initial increase in troponin in peripheral blood in patients with infarction occurs over 3–4 hours with a permanent increase for up to 2 weeks after infarction. In order to confirm or exclude myocardial damage, troponin T serum levels are repeated in the first 6–12 hours after severe chest pain [52].

The classification of myocardial infarction in five types was introduced in 2007 and established the clinical criteria for its exact differentiation [50]. Type 1 is related to a coronary plaque rupture, fissuring, or dissection with resulting intraluminal thrombosis. Type 2 myocardial infarction is secondary to myocardial ischemia resulting from increased oxygen demand or decreased supply. Type 3 myocardial infarction is linked to unexpected cardiac death when cardiac biomarkers are unavailable. Types 4 and 5 myocardial infarction are procedure related [53].

In the study of Saaby et al., [54] it was shown that the most significant number of patients with myocardial infarction come under Type 1 (72%). In patients with Type 1 myocardial infarction, changes in the ECG are seen either as the elevation or depression of the ST segment; the troponin T level also increases in the blood and serves as a diagnostic marker. The troponin T level in the blood is higher in patients with Type 1 myocardial infarction than Type 2 [55].

For manifestation of infarction, apart from lifestyle, a genetic background of myocardial infarction is also essential. A positive family history of myocardial infarction is a major cardiovascular risk factor [56]. Coronary artery disease and myocardial infarction have a genetic background in 50–60% of cases. Many genes are found in the genetic background of myocardial infarction. Whole genome association studies have revealed many variants of genes associated with increased risk for myocardial infarction [56]. So far the most frequently explored genes with increased risk for myocardial infarction are involved in the metabolic pathways of lipid metabolism and development of type 2 diabetes. The relationship between the circadian rhythm genes and the onset of myocardial infarction will be discussed below.
6. Myocardial infarction and circadian rhythm

Many cardiovascular events and diseases have a circadian pattern of appearance. The normal circadian blood pressure shows the two highest values during the day, around 9 am and 7 pm, while there is a slight decrease around 3 pm. It is considered that circadian variations in the tone of coronary vessels and endothelial function play an essential role in the onset of myocardial infarction. As myocardial infarction is significant medical stress, it causes increased cortisol levels in plasma [3]. In the acute phase of myocardial infarction, the phase of the circadian clock in the ischemic part of the heart differs from the non-ischemic part of the heart. The arrhythmia may occur because of the difference in the phase of the rhythm, or different expressions of the circadian clock genes. The loss of synchronization of the circadian rhythm between organs or tissues occurs more often than we would expect [4]. Circadian regulation of physiological processes is regulated locally. Peripheral tissue clocks control tissue-specific expression [27].

Homeostatic changes, gene expression changes, and external triggers can cause a stressful environment and cause damage to the atherosclerotic plaque in the coronary arteries in the morning, when prothrombin is increased [57]. Many intrinsic vasoactive and cardioactive substances, such as angiotensin II, melatonin, plasminogen activator inhibitor 1 (PAI-1), glucocorticoids, epinephrine, norepinephrine, and nitrogen oxide, show a specific circadian pattern. The fibrinolytic system, which regulates PAI-1, shows a circadian pattern of occurrence in both healthy patients and those with ischemic heart disease. The concentration and activity of PAI-1 depend on the circadian rhythm and are the highest in the morning [28]. CLIF (Cycle-Like Factor) expression in endothelial cells creates heterodimers with CLOCK protein, and binds to the E-box of the PAI-1 gene promoter and promotes its expression, while PER2 and CRY1 inhibit expression of PAI-1 by blocking heterodimer CLOCK-CLIF. CLIF controls the circadian rhythm of PAI-1 in endothelial cells, which might explain the higher incidence of myocardial infarction in the morning [26, 58]. As a result of this, the fibrinolytic system in patients with MI might be a potential goal for chronotherapy, to treat acute cardiovascular events. The circadian clock regulates the endothelial response to vascular injury. The main factor that can be affected by potential chronotherapy is PAI-1 because it is a crucial fibrinolysis inhibitor [59]. Chronotherapy includes the accurate timing of drug taking and can improve the therapeutic efficacy of the drug, while limiting its toxicity [41]. That is why many studies support chronotherapy for cardiovascular disease by limiting pathogenesis and improving treatment after the occurrence of acute cardiovascular events [59].

It is known that melatonin levels decrease during the night in coronary heart disease and infarction. Melatonin is an antioxidant that can inhibit the action of reactive oxygen radicals during heart ischemia. It also plays a vital role in regulating blood pressure, depending on the circadian rhythm. Animal studies have shown that animals with the pineal gland removed develop hypertension. Clinical examinations have shown that in patients with hypertension melatonin drugs taken daily before bedtime reduced blood pressure [3].

The appearance of myocardial infarction has two peaks during the day. The highest incidence of myocardial infarction is during the morning, and the second peak occurs late at night [60]. The beta blockers prevent increased sympathetic activity, catecholamine concentration, heart rate, blood pressure and lack of oxygen in the heart, and these are the physiological reasons for the existence of two peaks of myocardial infarction [57, 61].

Ischemia occurs in the morning due to increased oxygen demand, whereas in the evening it is due to decreased coronary blood flow. The appearance of myocardial infarction depends on ethnic origin, and the British differ from Asians in the
frequency of the infarction [3]. In the Mediterranean, the highest incidence of myocardial infarction is between midday and midnight, while in the UK the highest incidence is between midnight and midday [62]. Numerous factors might affect the later occurrence of infarction in the Mediterranean, such as the number of sunlight hours, inequality in the prevalence of risk factors for cardiovascular disease, and the habit of afternoon rest or ‘siesta’ [63]. It has also been noted that the incidence of myocardial infarction is higher in the winter [3]. The specific circadian pattern of infarction symptoms has been observed, and the correlation of the circadian rhythm gene with the infarction investigated. The role of the molecular circadian clock in myocardial activity was initially investigated on animal models. It has been observed that the clock gene mutations of the circadian rhythm affect the heart rate, myocardial contractility, energy metabolism, which altogether leads to ischemia [64, 65]. In contrast, variants of the Per2 gene in mice reduce the severity of the injury after myocardial infarction because it does not only reduce inflammatory response, but also reduces apoptosis, induces cardiovascular hypertrophy, and thus preserves cardiac function [65].

Different variations of circadian rhythm genes are associated with many risk factors for cardiovascular disease. Thus, CLOCK gene variations are associated with metabolic syndrome in humans, type 2 diabetes, and some with stroke [64, 66–68], while CRY2 and PER2 gene variations are associated with myocardial infarction [69]. Expression of CRY1 and PER2 genes in fatty tissue is associated with metabolic syndrome in humans [64, 70]. Metabolic syndrome is a significant risk factor for cardiovascular disease and contributes to the common pathophysiological processes leading to the development of diabetes and cardiovascular diseases [48]. Atherosclerotic changes in blood vessels in patients with diabetes are more severe than those with normal glucose concentration [71]. It has been shown that the risk of cardiovascular disease in diabetic patients is two to three times higher than in healthy subjects [72]. Patients with diabetes usually have a higher heart rate in sleep and lower heart rate variability over the day than people without diabetes, which causes unnecessary oxygen consumption in the myocardium, with reduced nutritional blood supply. Biological and epidemiological studies suggest a direct link between lifestyle and metabolic disorders [12], although the genetic and biochemical linkage of human circadian rhythm with metabolic disorders has not been fully explored. Accordingly, the importance of the circadian rhythm in maintaining ‘energy’ homeostasis and metabolism is evident.

6.1 Cardiomyocyte circadian clock

A peripheral clock is also found in cardiomyocytes, and the internal molecular mechanism of cardiomyocytes, such as the circadian clock, might contribute to cardiovascular disease [73]. Similar to SCN, cardiomyocytes have a circadian expression of clock genes in response to serum shock or norepinephrine. Several genes are associated with intracellular metabolism or physiological activity that has a circadian expression in cardiomyocytes [74]. After development, cardiomyocytes do not replicate, although they possess a meager and permanent rate of renewal. Cardiomyocytes renew cellular structure with their new proteins and membrane lipids every few weeks [75]. The ischemic precondition is an adaptation of cardiomyocytes to hypoxia, and once the heart has suffered an ischemic insult, cardiomyocytes become more resistant to MI because of PER2 and hypoxia inducible factor (HIF)-1α [74]. Circadian genes regulate a group of genes encoding for cardiac metabolic enzymes, and it is considered that a significant role of circadian genes in the heart is to synchronize cardiomyocyte metabolic activity with the availability of nutrients in the blood (i.e., feeding time) [29]. It is known that PER2 plays an essential role in carbohydrate metabolism during myocardial ischemia [76].
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The cardiomyocyte circadian clock affects the daily variations in the heart. Studies show that the cardiomyocyte circadian clock affects myocardial contractions, the metabolism and gene expression. This clock is vital since impairment of the cardiomyocyte circadian clock might significantly alter cardiac function, cardiovascular disease pathogenesis, and treatment strategies for cardiovascular diseases (e.g., chronopharmacology) [77]. Desynchronization between different cell types (e.g., cardiomyocytes, vascular smooth muscle cells, endothelial cells) could occur within the organs (e.g. the heart) during certain physiological or pathological conditions [78]. The cardiomyocyte circadian clock allows the heart to predict circadian rhythm by extracellular stimuli, allowing rapid and temporally response [77]. The cardiomyocyte circadian clock has a crucial role in mediating the daily rhythm in myocardial metabolism and affects the cardiovascular function [79]. The cardiomyocyte circadian clock changes during illness, and this molecular mechanism might affect the etiology of cardiovascular disease [78].

7. Conclusions

Circadian rhythm adjusts the physiological functions of an individual on a daily basis. Daily variations of physiological parameters in the cardiovascular system maintain cardiovascular function according to the needs of different activities during the day. This information suggests that we need to know not only how, but also when to treat heart disease, and also to treat pathological changes not only symptomatically but to treat non-symptomatic but potentially harmful changes in the circadian rhythm.

Understanding the pathophysiological processes involved in the onset of myocardial infarction requires additional studies to assess the crucial elements of the circadian rhythm. In today’s personalized medicine, knowledge of the circadian rhythm (i.e., the genetic background) of an individual can be significant for treatment and should be included as an essential part of the diagnostic process.

Conflict of interest

Authors declare no conflict of interest.

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