



**CHRONOBIOLOGY:
circadian rhythms in cardiovascular disease**

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Abstract

Every human being has, or rather carries within itself a clock that regulates their functions. And the science that helps us understand how this process happens is the Chronobiology, the area of biology that deals with the relation of living organisms with the passage of time. Thus, its main contribution is the idea that bodily functions are not constant, but expressed the rhythmicity of their physiological events. In this sense, it is seen so as to help people plan and understand their life cycle. In this context, this review paper aims to present how chronobiology is understood in cardiovascular diseases.

Keywords

Chronobiology.

**CRONOBIOLOGIA:
ritmos circadianos em doenças cardiovasculares**

Resumo

Todo ser humano tem ou, em vez disso, carrega dentro de si um relógio que regula suas funções. E a ciência que nos ajuda a entender como esse processo acontece é a Cronobiologia, a área da biologia que lida com a relação dos organismos vivos com a passagem do tempo. Assim, seu principal contributo é a idéia de que as funções corporais não são constantes, mas expressaram a rítmica de seus eventos fisiológicos. Nesse sentido, é visto de modo a ajudar as pessoas a planejar e entender seu ciclo de vida. Neste contexto, este artigo de revisão pretende apresentar como a cronobiologia é entendida nas doenças cardiovasculares.

Palavras-chave

Cronobiologia.

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Introduction

Chronobiology is the term applied to the study of how the body's rhythms are governed by our environment, from the solar power system, which cycles of day and night, or light and dark and the changes from one season to another (SON et al, 2008). It is the science that investigates biological rhythms with time as the main determinant of the evolutionary events responsible for anticipative homeostasis of living beings (VALE, VALE; CRUZ, 2009).

It is known that although the chronobiology is known in many countries, only from the 80's became the subject of studies in Brazil. Thus, this area of knowledge, use is made of chronobiological tools for understanding and interpreting also physiological events that occur regularly and vary over time (MORENO, 2008).

It is indispensable in chronobiology say there are three kinds of people or three types of individuals chronobiological. Accordingly, studies related to this area show that individuals have physiological variations during the day that can facilitate the implementation of activities (SEIBT et al). Thus, these aspects can be called chronotypes, which according to Horne and Ostberg (1976), individuals can be classified into three chronotypes considering individual differences in temporal allocation of sleep-wake cycles of biological rhythms. The chronotypes are morning, afternoon and indifferent. The individual is often characterized as a morning to sleep early and wake up early too, and in turn, shows a greater willingness to engage in activities during the morning. Moreover, the type of evening show a delay in the allocation of the sleep-wake cycle, as sleep and wake up later and report having greater willingness afternoon to carry out the activities, since the indifferent demonstrate schedule flexibility, which facilitates adaptation at times unconventional (FERREIRA, DE MARTINO, 2009).

Thus, one can say that the body is subjected to environmental changes such as light, temperature, nutrients, water, humidity, noise, toxins and pathogens. Despite these variations, several biological processes must be kept within physiological limits, so if it happens a failure to maintain the homeostasis of the organism, there is a tendency to develop disease (BRAY; YOUNG, 2008).



An essential aspect to understand this oscillation in the body is the biological clock. According to Moreno (2008), we perceive life on the optics of 3 watches: solar, biological and social. The solar corresponds to the alternation of day and night (light / dark), the social can be seen or felt as the beginning of the work day, as is explained by the biological alteration of the sleep cycle - waking, which is a marker rhythm.

The interaction with these three (3) watches determines the circadian rhythm with durability of approximately 24 hours, which we call day or better, corresponding 1 day ago. Corroborating this idea, Sandoval, Sanchez-de la Peña and Chavez-Negrete (2008), argue that biological periodicity for 1 day is known as circadian rhythm and that the most common explanation for the pace he is day / night.

In this sense, the system / circadian rhythm is proving an element of fundamental importance in human health and disease, since we can investigate and understand the timing existing at that pace. Thus cardiovascular tissues such as the heart and blood vessels, show a remarkable daily variation in gene expression, metabolism, growth and remodeling (SOLE; MARTINO, 2009).

1. Circadian rhythm

The circadian rhythm is an important key in linking behavior and metabolism, which synchronizes physiological processes, which is held as the earth's rotation on its axis (MARCHEVA et al., 2009).

The rhythms are generated and controlled by the biological clock that occurs in a complex network located in the Central Nervous System (CNS) (VAN SOMEREN, RIEMERSMA-VAN DER LEK, 2007; EKMEKCIOGLU; TOUITOU, 2011; CUTOLO, 2012). The regulation of this rhythm is under the influence of external synchronizer (Zeitgeber), the main consideration is undoubtedly light, which passes the information received to the suprachiasmatic nuclei (SCN) of the hypothalamus, located in the CNS (PERRIER; MANEN, 2011 , MARCHEVA et al., 2009).

The suprachiasmatic nuclei (SCN) are considered hypothalamic neural pacemaker that keeps the internal synchronization between the behavioral and physiological rhythm. (VALE, VALE, CROSS, 2009; DIBNER et al., 2010; JOHNSTON, 2012).



According Bray et al. (2008), many organisms have evolved circadian rhythms molecular mechanisms that are intracellular molecular mechanisms that allow individual cells realize the time of day. By doing so, circadian rhythms facilitate cellular responses to environmental stimuli in both the fast and temporally appropriate.

It is noteworthy that there are essential genes that generate oscillations and act on pace circadiano such as Per1, Per2, Per3, Bmal1, Clock, Cry genes and their products that include time engine maintenance. This downtime biological system also includes the peripheral cells, tissues and organs that are regulated and coordinated by the clock CNS (PORTALUPPI et al., 2011, SILVA; SATO; MARGOLIS, 2010).

On one hand, an interesting factor in relation to circadian rhythm is the integration of behavioral and physiological approaches, and the emerging knowledge in neural and peripheral tissues both in the pathogenesis of the disease (MAURY; RAMSEY, BASS, 2010).

Moreover, disturbances of circadian rhythms adversely affect normal growth, also the mechanisms remodeling disease, leading to severe abnormalities in the heart and vessels (SOLE; MARTINO, 2009; BRAY; YOUNG, 2008).

Scheer et al. (2009), state that the circadian misalignment, is a condition that is highly prevalent in shift workers, because there is a decrease of leptin, increased glucose and insulin, increased mean arterial pressure.

Still, changing patterns can lead to dysfunction of metabolic pathways, which may ultimately lead to a number of diseases, including obesity, metabolic syndrome, type 2 diabetic, cardiovascular disease, and cancer (SILVA; SATO; MARGOLIS, 2010).

2. Circadian rhythm in the cardiovasculares diseases

Heart diseases have emerged as a health problem in recent years (JHUND et al, 2009). Despite advances available, therapeutic interventions have had limited success in improving the long term survival of patients suffering from these diseases.

The mechanism of circadian rhythm cardiac function is described as cardiomyocytes, which are mediators known in circadian rhythmicity cardiac physiology (for example, heart rate, cardiac output) and pathophysiology (arrhythmias) (BRAY; YOUNG, 2008).



Importantly, they do not replicate the cardiomyocytes after development, although some evidence elucidate the idea of substitution progenitor cells (BERGMANN et al., 2009).

Furthermore, cardiomyocytes viewed protein and lipid membranes every few weeks and the effect renewing the cell structure (BUJA; CANDLE, 2008), for example, the half-life of the protein myosin in the contractile heart is considered approximately 15 days. However, contemporary medicine erroneously assumes that biology is an activity of continuous cleaning, constant throughout the day of 24h (SOLE; MARTINO, 2009).

The metabolism and myocardial contractile function are interrelated, so imbalances in energy metabolism adversely affects cardiac function (NEUBAUER, 2007). This is particularly relevant given the possibility that the circadian rhythm disorder in cardiomyocytes can significantly alter cardiac function, the pathogenesis of cardiovascular disease (CVD) (BRAY, et al., 2008).

Sole and Martino (2009), showed the assumption that elevations in blood pressure inadequate during the inactive phase of sleep may contribute significantly to the development of pathological hypertrophy, and ultimately, the contractile dysfunction i.e. cardiomyopathy.

In an experimental study using mice performed by Bray, et al. (2008), showed the existence of an intrinsic molecular mechanism of cardiomyocytes within which increases the probability or modulates the biological infarction and is essential for the responsiveness of the heart to fatty acids.

Although the authors, state that these findings support the idea that the circadian rhythm in cardiomyocyte allows the heart to anticipate circadian rhythms in extracellular stimuli (such as workload), thus allowing both rapid response and temporally appropriate.

Thus, the myocardial dyssynchrony with its environment via disruption of circadian rhythm intramyocellular and / or neurohumoral diurnal variations (occurring during diabetic mellitus, obesity, hypertension, ischemic heart disease) will probably accelerate the development of cardiovascular diseases (BRAY; YOUNG, 2008).

In other research proposed by Sandoval, Sanchez-de la Peña and Chavez-Negrete (2008), with the focus of verifying the timing of miocardiopadias in Mexico, using hospital records of Mexico City, it was evident that the pace of 7 and 3,5 days were the most gifts of this condition.



According to these authors, the rationale for such information may be related to the rhythms of social life in Mexico City and the other possibility would be that these rhythms of 7 days and multiple or submultiple reflect endogenous rhythms related to environmental factors in particular solar activity.

By knowing the time of day that a possible event can happen in the body presents a selective advantage in several biological layers, including tissues, cells and the whole organism. This information is essential to ensure rapid and appropriate responses in a correct way. So the key to this selective advantage is anticipation. However, the ability to prepare for an event before it occurs is critical to many aspects of life, including diseases cardiovasculares (DURGAN; YOUNG, 2010).

Studies have identified that the morning peak is evident in mortality rates among patients with Acute Myocardial Infarction (AMI), while others have identified different patterns (KOLETTIS et al., 2008).

The fact of myocardial infarction can happen in the morning explained because of the circadian variation in endogenous factors such as the autonomic nervous system function, concentrations of catecholamines in the blood, heart rate, blood pressure regulation, and platelet aggregation (OISHI, 2009).

Accordingly, differences in the circadian variation of AMI were reported in different world regions and ethnic groups. Although the peak is in the morning, most of the population. There are studies that show that most events of AMI in the Mediterranean Caucasians happened between noon and midnight, between these studies can highlight the research conducted with the Turkish population, which identified that the peak incidence of myocardial infarction was between 12:01 and 18:00 hours and from 00:01 to 06:00 hours (SARI, et al., 2009).

Thus, one can say that the circadian rhythm in AMI incidence peaking in the morning may not be applicable worldwide, but needs to be clarified and studied for each population.

For Holmes Jr et al. (2010), in studies of patients with AMI, there is a significant association between the time of onset and the circadian cycle, with the highest percentage (39%) of patients with early 8:00 to 15:00 h.



Further, Sole and Martino (2009), contribute to the study of the heart rhythm circadian saying that the expression of genes relevant to the metabolism cardiovascular growth and remodeling is dynamic, ie is not static and more, do not occur uniformly throughout the day-night cycle, since gene expression in the heart and blood vessels is different compared with day and night, for example, the growth and renewal seems to occur predominantly during the night.

Investigated other change made by Durgan and Young (2010) in the circadian rhythm was the effects of ischemia / reperfusion (I / R) on expression of genes circadian rhythm in the heart, using a mouse model with I / R, changes observed the rapid pace within the ischemic region versus nonischemic. This also suggests the interruption-desynchronization this circadian rhythm, may give rise to cardiovascular dysfunction.

Janszky et al. (2012) proposed a search using the registration information and knowledge regarding the admission of Swedes care unit of the heart, in that the data studied by these authors suggest that sleep, even on a modest deprivation and disturbances in sleep-wake cycle can increase the risk of AMI.

Finally, the circadian rhythm in the heart more precisely, cardiomyocytes has emerged as a molecular mechanism that influences various critical processes of the myocardium. This mechanism profoundly influences gene expression infarction, signaling, metabolism and contractile function.

Conclusion

Recognition of the importance of circadian rhythms in cardiovascular functions and their involvement in 24 hours in patterns of cardiovascular conditions and events, has been studied by chronobiology.

Accordingly models of animals used for experiments, including mice have shown the importance of the circadian rhythm in the differential regulation of cardiomyocytes during 24 hours of cardiac metabolism, and contractile function in ischemia / reperfusion, which tries to understand their role in pathogenesis of heart disease.

Another basic point was evidenced in studies disregulation circadian or circadian desincronization which may be profoundly important in the etiology and exacerbation of



vascular and cardiac disease, in which this can be extended to other tissues, including the central nervous system.

It is believed that future studies involving a greater understanding of circadian rhythms may help in treatment and consequently the quality of life for people who have a potential risk to cardiovascular disease.

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