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Circadian rhythm and heart disease - what is the link? A review

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Abstract
Introduction and purpose: Cardiovascular disease (CVD) is still the leading cause of death worldwide and causes 49% of mortality in Europe. This makes CVD is the most important reason for premature mortality and Disability Adjusted Life Years ("DALYS") in that continent. It is associated with variables such as blood pressure, heart rate, circulating catecholamines, markers of blood coagulation and vascular endothelial function which are dependent on different times of the day. The epidemiological data indicate that the biggest number of CVD incidents occur during the early morning hours. In this work we try to discuss the circadian rhythm and its impact on variables which, according to data, are most crucial on CV incident rate.

Brief description of the state of knowledge: The cardiovascular disease and mortality risk is associated with variables such as morning blood pressure, fluctuations in metabolism rate or even in immunological response. These variables are dependent on the circadian rhythm. This article covers the most crucial components affected by the daily fluctuations considering the heart according to the literature from the last five years.

Conclusions: This review highlighted the link between circadian rhythm and cardiovascular disease with the purpose of focusing on the most important clinically aspects of that machinery from blood pressure to inflammation. Despite all of these exciting findings which could possibly have future implications in the field of cardiology, there is still a significant need to explore this complicated relationship between the biological clock and the heart.

Keywords: Circadian rhythm, Blood pressure, Chronotherapy, Cardiovascular disease

Introduction:

1.1 Circadian rhythm

The Earth is rotating on its axis every 24 hours. Every living creature on the planet has a mechanism to anticipate environmental changes which are occurring on a daily basis. Circadian clocks in mammals are divided into a central clock- consisting of almost 20.000 neurons located in the hypothalamus- and a peripheral clock which can be found in almost every tissue[1]. The suprachiasmatic nucleus is a part of hypothalamus plays a key role in the circadian rhythm.The connections between suprachiasmatic nucleus and pituitary gland enable proper regulation of circadian rhythms, e.g. the secretion of cortisol in the morning [2]**.** These clocks are regulated by light received through the retina which primarily is transmitted to the master clock and afterwards to the peripheral clock via neurohumoral factors[3]. The core of the functionality of the clock is the negative feedback loop which include transcript factors: CLOCK, BMAL1, PER, CRY3. Protein products of these factors contribute to the biochemical cascade of the circadian rhythm[4]. Moreover, nine genes from coronary heart susceptibility were identified to predict the outcome of a linear combination of circadian rhythm pathway genes with R factor more than 0.7 [5].

Metabolism is a chemical process of converting food into energy or building blocks. Daily fluctuations in nutrient absorption, assimilation, substrate interconversion, and utilization are affecting, among others, body weight, body composition, glucose regulation, gut microbiome composition, lipid homeostasis etc.[6].

The rhythmicity of metabolism in the heart has been described focusing on lipids, carbohydrates or protein. In a healthy human heart at rest, 70% of energy comes from the oxidation of fatty acids, which are the main source of lipids for the human heart. Circadian rhythms also take part in this aspect. Myocardial triglyceride levels peak in the morning and are not affected by workload or triglyceride availability. Cardiac energy gain, derived from carbohydrates, stands at 20%. Furthermore, glycogenolysis has the greatest diurnal variability [7].

1.2 Cardiovascular incidents and its occurance

Cardiovascular disease (CVD) is still the leading cause of death worldwide and causes 49% of mortality in Europe, which is the most important reason of premature mortality and Disability Adjusted Life Years (“DALYS”) in Europe, thus creating a great public health importance on this topic [8]. It is associated with variables such as blood pressure, heart rate, circulating catecholamines, markers of blood coagulation and vascular endothelial function which are dependent on different times of the day. The epidemiological data indicate that the biggest number of CVD incidents occur during the early morning hours. Studies show that most sudden cardiac deaths and infarcts happen from 6 to 9 a.m. [9]

The REM phase during sleep is characterized by an increase of muscular tone, rapid eye movement and bursts of sympathetic activity which ends with higher blood pressure and increased heart rate[10]. Moreover, the sympathetic nervous system is more active during morning hours because of the early actions such as waking up, sudden change of posture after all night, psychological stress etc. Therefore, people are more at risk of developing CVD incidents before awakening. These daily fluctuations can be advantageous in healthy individuals but in susceptible ones, can raise the risk of CVD incident [1]. Interestingly, not only physiological sleep should be considered regulation of circadian rhythm. It has been found that anesthetics disrupt the expression of the circadian proteins including PER2, which could lead to sleep disturbances following general anesthesia[11].

In this review we try to discuss the circadian rhythm and its impact on variables which according to data are most crucial on CV incident rate.

2. State of knowledge

2.1 Blood pressure and circadian rhythm

Anomalies in blood pressure (BP) values are one of the reasons for CVD incidents therefore, it is necessary to find out the link between the changes in BP and circadian rhythm [12]. Data from 10 millions users of activity- recording devices show that during the night blood pressure decreases 10-15% and then rises so the highest values are noted in the morning [13]. People, who do not exhibit this type of “dip” of BP during the sleep, have non dipping hypertension which is connected with activation of renin-angiotensin- aldosterone system (RAAS). Individuals who do not exhibit a dip, i.e. a drop in blood pressure at rest, are referred to as 'non-dippers' [14]. There is also a ‘non-dipping’ hypertension, which has a significant association with the RAA system. The combination of these two factors, i.e. renal and cardiac dysfunction, increases the risk of cardiovascular mortality [15]. The nocturnal drop in blood pressure is directly associated with greater daytime sodium excretion compared to nocturnal excretion. Furthermore, the cardioprotective effect of SGLT2 inhibitors has been linked to the regulation of blood pressure and circadian rhythm[16]. The data presented above

highlight the role of the kidney and sodium metabolism in the normal maintenance of blood pressure and circadian rhythm.

Circadian rhythm disorders affect a large percentage of the population which is approximately 28% of the Western workforce [17]. A randomized crossover study was conducted on this group of patients. It has been shown that shift work increases levels of inflammatory factors such as CRP, IL-6, resistin, TNFα and their dysregulation of blood pressure through inflammatory activation and vascular endothelial dysfunction[14]. Numerous studies support the thesis of a connection between the circadian clock, kidneys, blood vessels, heart and blood pressure.

2.2 Immunology

Cardiovascular disease still remains the first cause of death worldwide, with an increasing prevalence in developing countries. However, the idea that this disease can occur as the reason for the inflammatory disturbance emerged in the late 1990s [18]. Studies conducted on mice showed that circadian machinery affects circulatory functions affecting RAAS, cardiac output, blood pressure and sympathetic nerve activity. That machinery is transcripted by CLOCK/ARNTL which was also discovered to increase expression of monocytes and its infiltration in the heart causing cardiac inflammation and fibrosis [19]. Circadian rhythm has been shown to impact the regulation of the NACHT, LRR, and PYD domains-containing protein 3 inflammasome, neutrophils, monocytes/macrophages, and T cells involved in cardiac repair [20,21].

Human studies have shown that lymphocyte, eosinophil and leukocyte counts vary from day to night and inversely correlate with cortisol levels. In addition, it should be mentioned that T and B lymphocytes peak at night and decrease in the morning when cortisol levels rise. Moreover, among shift- workers, production of C-reactive protein is significantly increased [22]. The production of cytokines, especially inflammatory cytokines, also shows circadian rhythmicity which has an important impact on the healing of damaged cells, e.g. in myocardial infarction. After myocardial cell damage, there is an increased production of the cytokines IL-1b and IL-18, which not only enhance the immune response, but also exacerbate cardiac damage[23]. In order to reduce myocardial degeneration, by lowering the cytokine storm, the substance SR9009, which affects one of the circadian clock factors, REV-ERB, has begun to be administered[24].

2.3 Atherosclerosis and Thrombosis

Atherosclerosis and thrombosis are the most common causes of heart diseases such as ischemic heart disease, acute myocardial infarction and heart failure [25]. Statistics from 2016 present the essence of the problem documenting that 14.3% of all deaths in Portugal were related to atherosclerosis [26]. As the increased blood pressure, thromboembolic events occur mostly in the morning [27]. This data suggest that the circadian rhythm may be another therapeutic target in the fight against heart diseases. In addition, the main clock located in the suprachiasmatic nucleus and peripheral clocks regulate the activity of specific tissues such as adipose tissue, immune system, liver, kidneys and vascular system [28].

Not only the levels of lipids and immune cells fluctuate daily, but also the nitric oxide (NO) which is produced by endothelium in the blood vessels [28,29]. In proper conditions, NO production is reduced in the morning. If this process is disturbed, as a consequence, the vessels will contract resulting in a blood pressure increase.

The imbalance between the coagulation system and fibrinolysis plays a key role in thrombosis. Clotting factors, platelets, platelet activation markers, D-dimers and markers of fibrinolysis reach peak levels in the early morning hours. This poses the greatest risk of homeostasis disturbance resulting in thromboembolic events[24].

2.4 Neurodegeneration

Circadian rhythms of heart rate and blood pressure are regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, which modulates the autonomic nervous system activity connected to the heart and blood vessels. Moreover, periodically released humoral mediators by the SCN as well as sleep are also important factors. Disturbance in cardiovascular circadian rhythms has great clinical implications, as it has been proved with increased morbidity and mortality[30].There is more data indicating that dementia and Alzheimer disease are associated with circadian disruption due to loss of suprachiasmatic nucleus (SCN) neurons and impaired function of light input pathways. Moreover, there is evidence for misalignment of neuronal activity in different brain regions, such as between the SCN and hippocampus[31]. Taking all that information into consideration we should focus on mental health, especially among the cardiological patients.

3. Therapy options

Studies suggest that infusion of ANP, BNP and CNP lead to vascular effects, causing vasodilation consequently lowering blood pressure [18]. Regulating sleep cycles can be crucial in preventing CV incidents.

Some studies indicate that sleep deprivation can contribute to gut dysbiosis as a result of HPA- axis activation. Metabolites of specific bacterial species which are growing in response to sleep loss are inducing fatigue and consequently promoting disturbed sleep cycles [32] The multicentered, prospective study conducted in 2020 on 19 084 hypertension patients showed that ingestion of the daily dose of hypertension medication in the bedtime resulted in a lower hazard ratio of CVD outcome compared to the group which were taking medication upon-waking treatment time [33]. Another study conducted in Japan on 6,359 patients which underwent 24-hours ambulatory blood pressure monitoring at baseline showed that disrupted circadian blood pressure rhythm (riser pattern, nighttime BP higher than daytime BP) was significantly associated with higher overall cardiovascular disease risk and especially heart failure compared with normal circadian rhythm [34]. This data indicates the importance of targeting cardiological medication on night fluctuations of blood pressure.

A promising therapeutic target is sirtuin therapy, which slows down aging and vascular degradation [35]. Sirtuin is an NAD + -dependent protein deacetylase synthesized by the SIRT1 gene[36].The enzyme increases the synthesis of NO in endothelial cells, leading to vasodilation, inhibiting the formation of foam cells, lowering the level of LDL, and above all, reducing chronic inflammation [28].

Secondary metabolites of plants - polyphenols, in addition to their antioxidant and anti-inflammatory effects, can modulate the amplitudes and oscillation period of circadian rhythm genes. Recently, resveratrol was found to be a SIRT1 activator, which can alleviate obesity and significantly reduce atherosclerotic lesions and improve lipidogram[37].

It is worth noting that scientists discovered a promising treatment concept that accelerates the healing of non-cardiac lesions by administering the substance SR9009. It affects one of the circadian clock factors, which is REV-ERB. Taking this drug after a myocardial infarction during the day will reduce degeneration and consequently reduce mortality[24]. This is a very promising treatment concept that, by reducing the adverse cytokine storm and limiting the immune response, may create a more favourable environment for healing of post-infarction lesions.

4. Conclusions

This review highlighted the link between circadian rhythm and cardiovascular disease with the purpose of focusing on the four most crucial variables according to the literature from the last five years. All these findings confirm the statement that keeping circadian rhythm properly functioning is an important factor in lowering the rate of CVD incidents among patients. Cardiological patients should keep in mind that a healthy diet, working during the day without the shift system, proper rest during the night and leading can help with reducing the risk of stroke, infarct or sudden cardiac death which occur mostly in the morning. According to data, disturbance in sleep patterns can result in an immunological response which causes inflammation affecting the heart making it more vulnerable to CVD incidents. Human metabolism is affected by the time of the day. The heart is dependent on the energy sources such as lipids which show fluctuations in their levels due to the circadian rhythm. This knowledge could be useful in proposing new therapies for patients at risk of CVD. Studies suggest that giving heart medication before night sleep and overall regulating night's blood pressure fluctuations can significantly lower the risk of CVD incidents. Moreover, data indicates that intervention with substances contributing to vasodilation of blood vessels can lower the blood pressure. Additionally, this knowledge should be implicated during the preparations for the cardiological operations since the outcome for the patients could be affected by disruption of the circadian rhythm due to anesthesia. However, due to the complicated physiological mechanisms which are part of the circadian rhythm, it is necessary to conduct more studies focusing on the relationship described in this article. Discovering new links in the area could potentially develop new therapies for cardiological patients and consequently lower the rate of the leading cause of death worldwide.

References

1. Thosar SS, Butler MP, Shea SA. Role of the circadian system in cardiovascular disease. J Clin Invest. 2018;128(6):2157-2167. doi:10.1172/JCI80590

2. Ruan W, Yuan X, Eltzschig HK. Circadian rhythm as a therapeutic target. Nat Rev Drug Discov. 2021;20(4):287-307. doi:10.1038/s41573-020-00109-w

3. Crnko S, Du Pré BC, Sluijter JPG, Van Laake LW. Circadian rhythms and the molecular clock in cardiovascular biology and disease. Nat Rev Cardiol. 2019;16(7):437-447. doi:10.1038/s41569-019-0167-4

4. Black N, D'Souza A, Wang Y, et al. Circadian rhythm of cardiac electrophysiology, arrhythmogenesis, and the underlying mechanisms. Heart Rhythm. 2019;16(2):298-307. doi:10.1016/j.hrthm.2018.08.026

5. Yan X, Huang Y, Wu J. Identify Cross Talk Between Circadian Rhythm and Coronary Heart Disease by Multiple Correlation Analysis. J Comput Biol. 2018;25(12):1312-1327. doi:10.1089/cmb.2017.0254

6. Chaix A, Manoogian ENC, Melkani GC, Panda S. Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases. Annu Rev Nutr. 2019;39:291-315. doi:10.1146/annurev-nutr-082018-124320

7. Zhang L, Jain MK. Circadian regulation of cardiac metabolism. J Clin Invest. 2021;131(15):e148276. doi:10.1172/JCI148276

8. Francula-Zaninovic S, Nola IA. Management of Measurable Variable Cardiovascular Disease' Risk Factors. Curr Cardiol Rev. 2018;14(3):153-163. doi:10.2174/1573403X14666180222102312

9. Booth JN 3rd, Jaeger BC, Huang L, et al. Morning Blood Pressure Surge and Cardiovascular Disease Events and All-Cause Mortality in Blacks: The Jackson Heart Study. Hypertension. 2020;75(3):835-843. doi:10.1161/HYPERTENSIONAHA.119.14233

10. Peter-Derex L, Derex L. Wake-up stroke: From pathophysiology to management. Sleep Med Rev. 2019;48:101212. doi:10.1016/j.smrv.2019.101212

11. Bartman CM, Eckle T. Circadian-Hypoxia Link and its Potential for Treatment of Cardiovascular Disease. Curr Pharm Des. 2019;25(10):1075-1090. doi:10.2174/1381612825666190516081612

12. Luo D, Cheng Y, Zhang H, et al. Association between high blood pressure and long term cardiovascular events in young adults: systematic review and meta-analysis. BMJ. 2020;370:m3222. Published 2020 Sep 9. doi:10.1136/bmj.m3222

13. Mehra R. Sleep apnea and the heart. Cleve Clin J Med. 2019;86(9 Suppl 1):10-18. doi:10.3949/ccjm.86.s1.03

14. Douma LG, Gumz ML. Circadian clock-mediated regulation of blood pressure. Free Radic Biol Med. 2018;119:108-114. doi:10.1016/j.freeradbiomed.2017.11.024

15. Ohashi, N., Isobe, S., Ishigaki, S. et al. Circadian rhythm of blood pressure and the renin–angiotensin system in the kidney. Hypertens Res 40, 413–422 (2017). https://doi.org/10.1038/hr.2016.166

16. Rahman, A., Hitomi, H. & Nishiyama, A. Cardioprotective effects of SGLT2 inhibitors are possibly associated with normalization of the circadian rhythm of blood pressure. Hypertens Res 40, 535–540 (2017). https://doi.org/10.1038/hr.2016.193

17. Khaper N, Bailey CDC, Ghugre NR, et al. Implications of disturbances in circadian rhythms for cardiovascular health: A new frontier in free radical biology. Free Radic Biol Med. 2018;119:85-92. doi:10.1016/j.freeradbiomed.2017.11.006

18. Fioranelli M, Bottaccioli AG, Bottaccioli F, Bianchi M, Rovesti M, Roccia MG. Stress and Inflammation in Coronary Artery Disease: A Review Psychoneuroendocrineimmunology-Based. Front Immunol. 2018;9:2031. Published 2018 Sep 6. doi:10.3389/fimmu.2018.02031

19. Yoshida Y, Matsunaga N, Nakao T, et al. Alteration of circadian machinery in monocytes underlies chronic kidney disease-associated cardiac inflammation and fibrosis. Nat Commun. 2021;12(1):2783. Published 2021 May 13. doi:10.1038/s41467-021-23050-x

20. Aziz IS, McMahon AM, Friedman D, Rabinovich-Nikitin I, Kirshenbaum LA, Martino TA. Circadian influence on inflammatory response during cardiovascular disease. Curr Opin Pharmacol. 2021;57:60-70. doi:10.1016/j.coph.2020.11.007

21. Epelman, S., Liu, P. & Mann, D. Role of innate and adaptive immune mechanisms in cardiac injury and repair. Nat Rev Immunol 15, 117–129 (2015). https://doi.org/10.1038/nri3800

22. Morris CJ, Purvis TE, Mistretta J, Hu K, Scheer FAJL. Circadian Misalignment Increases C-Reactive Protein and Blood Pressure in Chronic Shift Workers. Journal of Biological Rhythms. 2017;32(2):154-164. doi:10.1177/0748730417697537

23. Toldo, S., Abbate, A. The NLRP3 inflammasome in acute myocardial infarction. Nat Rev Cardiol 15, 203–214 (2018). https://doi.org/10.1038/nrcardio.2017.161

24. Wang S., Lin Y., Yuan X., Li F., Guo L., Wu B.: REV-ERBalpha integrates colon clock with experimental colitis through regulation of NF-kappaB/NLRP3 axis. Nat Commun 2018; 9: pp. 4246.

25. Soehnlein O, Libby P. Targeting inflammation in atherosclerosis - from experimental insights to the clinic. Nat Rev Drug Discov. 2021;20(8):589-610. doi:10.1038/s41573-021-00198-1

26. Costa J, Alarcão J, Araujo F, et al. The burden of atherosclerosis in Portugal. Eur Heart J Qual Care Clin Outcomes. 2021;7(2):154-162. doi:10.1093/ehjqcco/qcaa060

27. Kumar, S.; Kumar, N.; Kumar, H.; Niazi, R.A.; Rashid, M.F. Circadian Variation In The Onset Of Acute Myocardial Infarction In Diabetics. J. Ayub Med. Coll. Abbottabad Jamc 2018, 30, 71–73.

28. Man AWC, Li H, Xia N. Circadian Rhythm: Potential Therapeutic Target for Atherosclerosis and Thrombosis. Int J Mol Sci. 2021;22(2):676. Published 2021 Jan 12. doi:10.3390/ijms22020676

29. Pan X, Mota S, Zhang B. Circadian Clock Regulation on Lipid Metabolism and Metabolic Diseases. Adv Exp Med Biol. 2020;1276:53-66. doi:10.1007/978-981-15-6082-8_5

30. Fishbein AB, Knutson KL, Zee PC. Circadian disruption and human health. J Clin Invest. 2021;131(19):e148286. doi:10.1172/JCI148286

31. Baschieri F, Cortelli P. Circadian rhythms of cardiovascular autonomic function: Physiology and clinical implications in neurodegenerative diseases. Auton Neurosci. 2019;217:91-101. doi:10.1016/j.autneu.2019.01.009

32. Matenchuk BA, Mandhane PJ, Kozyrskyj AL. Sleep, circadian rhythm, and gut microbiota. Sleep Med Rev. 2020;53:101340. doi:10.1016/j.smrv.2020.101340

33. Hermida RC, Crespo JJ, Domínguez-Sardiña M, et al. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J. 2020;41(48):4565-4576. doi:10.1093/eurheartj/ehz754

34. Kario K, Hoshide S, Mizuno H, et al. Nighttime Blood Pressure Phenotype and Cardiovascular Prognosis: Practitioner-Based Nationwide JAMP Study [published correction appears in Circulation. 2020 Dec 22;142(25):e632]. Circulation. 2020;142(19):1810-1820. doi:10.1161/CIRCULATIONAHA.120.049730

35. Begum MK, Konja D, Singh S, Chlopicki S, Wang Y. Endothelial SIRT1 as a Target for the Prevention of Arterial Aging: Promises and Challenges. J Cardiovasc Pharmacol. 2021 Dec 1;78(Suppl 6):S63-S77. doi: 10.1097/FJC.0000000000001154. PMID: 34840264.

36. Xu W, Li L, Zhang L. NAD+ Metabolism as an Emerging Therapeutic Target for Cardiovascular Diseases Associated With Sudden Cardiac Death. Front Physiol. 2020 Aug 13;11:901. doi: 10.3389/fphys.2020.00901. PMID: 32903597; PMCID: PMC7438569.

37. Liu, F.; Zhang, X.; Zhao, B.; Tan, X.; Wang, L.; Liu, X. Role of Food Phytochemicals in the Modulation of Circadian Clocks. J. Agric. Food Chem. 2019, 67, 8735–8739.