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Chronotherapy in cardiovascular medicine: Optimizing treatment timing based on circadian rhythms

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ABSTRACT

Chronotherapy, which leverages the circadian rhythms of biological processes to optimize medication timing, has shown potential benefits in cardiovascular medicine. This review explores the scientific rationale and clinical evidence supporting chronotherapy for hypertension, ischemic heart disease, and heart failure, aiming to enhance treatment efficacy while minimizing adverse effects. Emerging technologies, such as wearable devices for real-time circadian monitoring, offer further precision in aligning treatments with patients' natural rhythms. Nevertheless, challenges in implementing chronotherapy on a personalized level remain, underscoring the need for continued research and development in this field.

KEYWORDS

Chronotherapy; Cardiovascular medicine; Circadian rhythm; Drug timing; Ischemic heart disease; Heart failure

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Introduction

The cardiovascular system closely aligns with internal circadian rhythms, approximately 24-hour cycles that regulate various biological processes according to environmental patterns, primarily light and darkness. These rhythms are governed by a central "clock" in the brain known as the suprachiasmatic nucleus (SCN), which orchestrates the timing of physiological functions across the body. This clock influences cardiovascular activities like blood pressure management, heart rate, and vascular tone through both the autonomic nervous system and hormonal signals, causing predictable changes throughout the day and night [1].

The circadian system adjusts blood pressure and heart rate in response to environmental cues, peaking at certain times to meet physical and mental requirements. For instance, the early morning hours are characterized by increased sympathetic nervous system activity, elevating blood pressure and heart rate as the body gets ready to be active. Such fluctuations can elevate the risk of cardiovascular incidents, as the cardiovascular system faces greater stress during these times [2]. The circadian rhythm additionally affects blood flow, arterial flexibility, and blood clotting patterns, which can raise cardiovascular risk depending on the time of day. Disturbances to these natural rhythms, whether from lifestyle choices, shift work, sleep disorders, or underlying health issues, have been linked to a heightened risk of cardiovascular problems, as a disconnect between internal rhythms and external demands can create precarious periods [3].

Chronotherapy seeks to utilize this time-dependent variability in cardiovascular physiology to enhance treatment effectiveness. By timing drug administration to coincide with moments when the body is most receptive, chronotherapy aims to optimize treatment benefits while minimizing side effects. This approach aligns medical treatment with natural biological cycles and addresses the specific timing needs of various cardiovascular disorders [4].

Circadian Rhythms and Cardiovascular Physiology

The suprachiasmatic nucleus, located in the hypothalamus, governs the body's internal clock, which manages circadian rhythms affecting nearly every physiological system, including cardiovascular health. For instance, blood pressure typically follows a daily rhythm, exhibiting a "dipping" pattern during sleep and a rise upon waking, primarily due to increased cortisol levels and sympathetic nerve activity. This morning surge aligns with a peak in cardiovascular incidents, such as myocardial infarctions and strokes. Chronotherapy seeks to mitigate the risks associated with these natural rhythms by timing medications to counteract them, ultimately enhancing patient outcomes and the efficacy of drugs [5].

Recent research indicates that the effectiveness of cardiovascular medications can vary based on the timing of administration. For instance, angiotensin receptor blockers (ARBs) and ACE inhibitors tend to be more effective when taken at night rather than in the morning. This timing aligns with the body's natural rhythms and helps reduce the early morning spike in blood pressure that often precedes cardiovascular events [6].

The circadian system also influences heart rate variability, platelet activity, and vascular tone throughout the day. Recognizing these patterns allows healthcare providers to optimize treatment regimens. For instance, antiplatelet medications may be more effective when timed to address the morning surge in platelet activity, while statins might be more effective if taken in the evening to align with peak cholesterol production [7].

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Personal factors such as age, work schedules, and concurrent health conditions can all impact circadian rhythms, necessitating customized chronotherapeutic strategies. For example, shift workers may need specially tailored medication schedules to accommodate their irregular sleep-wake patterns. Similarly, patients with diabetes or sleep disorders may require distinct timing approaches due to their altered circadian rhythms [8].

Chronotherapy in Hypertension Management

Chronotherapy has demonstrated encouraging outcomes in managing hypertension. Numerous studies, including the prominent MAPEC trial, have indicated that administering antihypertensive drugs at night instead of in the morning enhances blood pressure regulation and lowers the risk of cardiovascular incidents in the early morning. The MAPEC trial, which monitored over 2,000 patients, found that evening dosages of antihypertensives led to superior blood pressure management and a significantly reduced likelihood of cardiovascular events compared to morning administration. Nighttime dosing appeared particularly beneficial for individuals with a "non-dipping" blood pressure pattern, which correlates with a higher risk of cardiovascular disease. This research illustrates that chronotherapy may be effective in customizing hypertension treatments to align with individual circadian rhythms, improving effectiveness and minimizing side effects [9].

Further research has shown that specific categories of antihypertensive medications may experience enhanced effects when taken at night. For instance, ACE inhibitors and ARBs may demonstrate greater effectiveness when administered in the evening, potentially due to their interaction with the natural rhythm of the renin-angiotensin-aldosterone system. Likewise, calcium channel blockers taken in the evening promote better 24-hour blood pressure regulation, especially during the vital early morning hours [10].

Implementing chronotherapy in hypertension management requires a careful assessment of patient-specific characteristics. For instance, elderly patients often exhibit different circadian patterns for blood pressure, necessitating tailored timing strategies. Patients with diabetes, who frequently present with atypical blood pressure rhythms, might gain the most advantages from taking antihypertensive medications in the evening [11].

Advancements in modern technology have significantly enhanced our capacity to monitor and refine chronotherapeutic treatments. Ambulatory blood pressure monitoring systems can track the blood pressure patterns of individual patients over a day, enabling healthcare providers to pinpoint optimal medication schedules. Smart pill dispensers and mobile applications can help patients adhere to consistent medication timings, which enhances treatment compliance and outcomes [12].

Application in Ischemic Heart Disease and Heart Failure

Chronotherapy has the potential to help individuals with ischemic heart disease mitigate the morning spike in ischemia episodes by timing the administration of medications like beta-blockers or antiplatelets to align with early morning physiological changes. Patients with heart failure may see improvements from medications scheduled according to their circadian rhythms. Research indicates that aligning diuretic and beta-blocker regimens with patients' circadian patterns may enhance treatment effectiveness, although additional investigation is necessary to validate these results. Studies on beta-blockers show that adjusting the dosage to align with the body's physiological needs can decrease the risk of morning cardiac strain. Although promising, these approaches require more extensive research to confirm their overall effectiveness and determine the best timing for specific medications [7].

Recent studies have explored the timing of antiplatelet drugs in relation to daily fluctuations in platelet activity. Increased platelet aggregability during morning hours suggests that strategically timing antiplatelet medications could enhance their protective effects against acute coronary incidents. For instance, taking aspirin in the evening might be more effective at preventing early morning platelet activation than a morning dose [13].

In the management of heart failure, the timing of loop diuretics can play a crucial role in maintaining fluid balance and alleviating symptoms. Administering diuretics in the evening may help alleviate nighttime fluid retention and related breathing issues, especially for patients experiencing sleep-disordered breathing. However, this tactic must be weighed against potential sleep disturbances caused by frequent urination [14].

Chronotherapy also encompasses the scheduling of rhythm control medications for those with atrial fibrillation. Evidence suggests that the timing of antiarrhythmic drugs can be optimized to minimize episodes linked to circadian rhythms. For example, certain individuals may experience increased arrhythmic events at specific times of the day, indicating that medication timing could be adjusted accordingly [5].

When implementing chronotherapy, it is essential to consider individual patient factors such as sleeping patterns, daily routines, and coexisting conditions. Shift workers and those with irregular sleep cycles might need tailored medication scheduling strategies. Additionally, conditions like diabetes or kidney disease may affect the optimal timing of cardiovascular drugs [15].

Role of Technology in Personalized Chronotherapy

Recent developments in wearable technology and digital health monitoring have created new possibilities for personalized chronotherapy implementation. Wearable devices like smartwatches that track heart rate variability, blood pressure, and sleep habits allow for the real-time observation of patients' circadian rhythms. These insights enable healthcare providers to more effectively adjust medication timing, potentially enhancing the success and customization of chronotherapy. Nevertheless, challenges such as data privacy, costs, and integration into standard clinical practice hinder the broader use of these technologies [12].

Smart pill dispensers linked to these monitoring systems present compelling options for improving treatment adherence. These devices can automatically modify medicine release times

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based on individual patient data, ensuring optimal therapeutic timing while alleviating the complexity of medication schedules for patients [16]. Continuous glucose monitoring systems, paired with cardiovascular tracking devices, offer valuable insights into the connections between metabolic trends and cardiovascular health. This integration supports the optimization of drug scheduling for diabetes and cardiovascular conditions, particularly for patients with multiple health issues [17].

The advent of mobile health applications has heightened patient engagement in chronotherapy. These apps can track medication timing, issue reminders, and gather patient-reported outcomes, painting a detailed picture of treatment efficacy. Some applications now factor in environmental elements like light exposure and physical activity, which can influence circadian rhythms [18]. Telemedicine technologies have advanced to facilitate the adoption of chronotherapy by enabling remote monitoring and adjustments to treatment schedules. Healthcare providers can analyze patient data trends and modify medication timing in real time, reducing the necessity for frequent in-person appointments [19].

Practical Challenges and Future Directions

The broad use of chronotherapy in treating cardiovascular conditions faces several practical challenges, even with promising results. Variations in individual circadian rhythms due to shift work, lifestyle choices, and genetic factors complicate the standardization of chronotherapeutic methods. Additionally, ensuring patient adherence to evening or nighttime dosages can be challenging, particularly for those with complex medication regimens. Moreover, current healthcare systems lack established protocols for circadian-based treatments, highlighting the need for further randomized controlled trials to create standardized methods [4]. Future studies should focus on creating adaptive, patient-centric chronotherapeutic models utilizing data from wearable technology and genetic analysis. Cooperation among cardiologists, chronobiologists, and digital health experts could lead to more detailed guidelines that facilitate personalized therapeutic strategies in cardiovascular care [20].

The integration of pharmacogenomics with chronotherapy is an evolving area. Genetic differences in circadian clock genes can affect how drugs are metabolized and their effectiveness, suggesting that genetic assessment might enhance medication customization. For instance, variations in clock genes could influence the optimal timing for administering antihypertensive medications [21]. Educating healthcare providers is a significant hurdle. Many physicians have not received formal education on the principles of chronotherapy, making them reluctant to implement time-based treatment strategies. Developing thorough educational initiatives and clinical support tools could bridge this knowledge gap [22]. Economic factors also play a role in the adoption of chronotherapy. Insurance may offer limited coverage for specialized monitoring devices and frequent adjustments to medication schedules. Therefore, cost-effectiveness analyses are needed to demonstrate the long-term advantages of chronotherapeutic approaches in reducing cardiovascular issues [23]. The creation of advanced drug delivery systems that can automatically dispense medications at the right times holds promise. These innovations could address adherence challenges while ensuring accurate drug administration. However, developing and implementing them requires significant investment and regulatory approval [15].

International collaboration and the standardization of chronotherapy strategies are essential. Different regions may require tailored approaches due to variations in daylight patterns and cultural practices, necessitating region-specific guidelines while upholding scientific integrity [24].

Conclusions

Chronotherapy offers promising advancements in cardiovascular treatment by aligning medication schedules with patients' circadian rhythms. Research demonstrates its benefits for hypertension and indicates potential for ischemic heart disease and heart failure, though practical challenges and individual variability call for further study. Advances in wearable technology and personalized care may help position chronotherapy as a vital tool in cardiovascular management, enhancing patient outcomes and quality of life.

Integrating chronotherapy with precision medicine represents a significant shift, allowing treatment plans to account for genetic and circadian factors, which is particularly beneficial for patients with complex cardiovascular issues or comorbidities. Recent developments in time-released medications and smart drug delivery systems could further address medication timing challenges, especially for patients with cognitive difficulties or intricate schedules. Additionally, understanding environmental influences like light exposure, temperature, and social patterns can refine chronotherapeutic strategies. Patient education through apps and interactive portals may also improve awareness and adherence, supporting the effective application of chronotherapy in cardiovascular care.

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Disclosure Statement

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References

1. Thosar SS, Butler MP, Shea SA. Role of the circadian system in cardiovascular disease. J Clin Invest. 2018;128(6):2157-2167. https://doi.org/10.1172/JCI80590
2. Thosar SS, Shea SA. Circadian control of human cardiovascular function. Curr Opin Pharmacol. 2021;57:89-97. https://doi.org/10.1016/j.coph.2021.01.002
3. Lin J, Kuang H, Jiang J, Zhou H, Peng L, Yan X, et al. Circadian rhythms in cardiovascular function: Implications for cardiac diseases and therapeutic opportunities. Medical Science Monitor: Int J Clin Exp Med. 2023;29:e942215. https://doi.org/10.12659/MSM.942215
4. Festus ID, Spilberg J, Young ME, Cain S, Khoshnevis S, Smolensky MH, et al. Pioneering new frontiers in circadian medicine chronotherapies for cardiovascular health. TEM. 2024;35(7):607-623. https://doi.org/10.1016/j.tem.2024.02.011
5. Smolensky MH, Hermida RC, Geng YJ. Chronotherapy of cardiac and vascular disease: timing medications to circadian rhythms to optimize treatment effects and outcomes. Curr Opin Pharmacol.

https://doi.org/10.61577/ijcri.2024.100008

2021;57:41-48. https://doi.org/10.1016/j.coph.2020.10.014
6. Potucek P, Klimas J. Chronopharmacology of high blood pressure—a critical review of clinical evidence. Eur Pharm J. 2019;66(2):32-36. https://doi.org/10.2478/afpuc-2019-0017
7. Buurma M, Van Diemen JJ, Thijs A, Numans ME, Bonten TN. Circadian rhythm of cardiovascular disease: the potential of chronotherapy with aspirin. Front Cardiovasc Med. 2019;6:84. https://doi.org/10.3389/fcvm.2019.00084
8. Kalmukova O, Kyryk V, Dzerzhynsky M. Circadian Rhythms and Personalized Strategies For Anti-Aging Therapies. AAEE. 2022;1(1):19-27. https://doi.org/10.56543/aaeeu.2022.1.1.03
9. Kim HJ, Jo SH. Nighttime administration of antihypertensive medication: a review of chronotherapy in hypertension. Korean J Intern Med. 2024;39(2):205. https://doi.org/10.3904/kjim.2023.304.
10. Hermida RC, Fernandez JR, Mojon A. Current evidence on the circadian-time-dependent effects of hypertension medications and their combinations in relation to findings of MAPEC and Hygia Chronotherapy Trial. Chronobiol Int. 2020;37(5):751-758. https://doi.org/10.1080/07420528.2020.1771356
11. Burnier M, Kreutz R, Narkiewicz K, Kjeldsen S, Oparil S, Mancia G. Circadian variations in blood pressure and their implications for the administration of antihypertensive drugs: is dosing in the evening better than in the morning?. J Hypertens. 2020;38(8): 1396-406. https://doi.org/10.1097/HJH.0000000000002532
12. Kim DW, Zavala E, Kim JK. Wearable technology and systems modeling for personalized chronotherapy. Curr Opin Syst Biol. 2020;21:9-15. https://doi.org/10.1016/j.coisb.2020.07.007.
13. Van Diemen JJ, Madsen MC, Vrancken P, De Bie K, van der Bom JG, Veen G, et al. Evening aspirin intake results in higher levels of platelet inhibition and a reduction in reticulated platelets-a window of opportunity for patients with cardiovascular disease?. Platelets. 2021; 32(6):821-827. https://doi.org/10.1080/09537104.2020.1809643
14. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75(10):1178-1195. https://doi.org/10.1016/j.jacc.2019.12.059
15. Amiama-Roig A, Verdugo-Sivianes EM, Carnero A, Blanco JR. Chronotherapy: circadian rhythms and their influence in cancer therapy. Cancers. 2022;14(20):5071. https://doi.org/10.3390/cancers14205071
16. Almansouri NE, Awe M, Rajavelu S, Jahnavi K, Shastry R, Hasan A, et al. Early Diagnosis of Cardiovascular Diseases in the Era of Artificial Intelligence: An In-Depth Review. Cureus. 2024;16(3). https://doi.org/10.7759/cureus.55869
17. Zijp TR, Touw DJ, van Boven JF. User acceptability and technical robustness evaluation of a novel smart pill bottle prototype designed to support medication adherence. Patient Prefer Adherence. 2020;625-634. https://doi.org/10.2147/PPA.S240443
18. Pauley ME, Tommerdahl KL, Snell-Bergeon JK, Forlenza GP. Continuous glucose monitor, insulin pump, and automated insulin delivery therapies for type 1 diabetes: an update on potential for cardiovascular benefits. Curr Cardiol Rep. 2022;24(12):2043-2056. https://doi.org/10.1007/s11886-022-01799-x.
19. Ahmed A, Mutahar M, Daghrery AA, Albar NH, Alhadidi IQ, Asiri AM, et al. A Systematic Review of Publications on Perceptions and Management of Chronic Medical Conditions Using Telemedicine Remote Consultations by Primary Healthcare Professionals April 2020 to December 2021 During the COVID-19 Pandemic. Medical science monitor: Int J Clin Exp Med. 2024;30:e943383. https://doi.org/10.12659/MSM.943383
20. Lee Y, Field JM, Sehgal A. Circadian rhythms, disease and chronotherapy. J Biol Rhythms. 2021;36(6):503-531. https://doi.org/10.1177/07487304211044301
21. Koyanagi S. Chrono-pharmaceutical approaches to optimize dosing regimens based on the circadian clock machinery. Biol Pharm Bull. 2021;44(11):1577-1584. https://doi.org/10.1248/bpb.b21-00476
22. Fujimura A, Ushijima K. Understanding the role of chronopharmacology for drug optimization: what do we know?. Expert Rev Clin Pharmacol. 2023;16(7):655-668. https://doi.org/10.1080/17512433.2023.2233438
23. Casciaro S, Massa L, Sergi I, Patrono L. A smart pill dispenser to support elderly people in medication adherence. In2020 5th International Conference on Smart and Sustainable Technologies (SpliTech). IEEE. 2020;1-6. https://doi.org/10.23919/SpliTech49282.2020.9243773
24. Marcu LG. Circadian rhythm-based cancer therapy in randomised clinical trials. Expert Rev Anticancer Ther. 2024;24(1-2):29-39. https://doi.org/10.1080/14737140.2023.2298835

https://doi.org/10.61577/ijcri.2024.100008