JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Review on chronopharmacology of cardiovascular system

[1] Gargi H. Maharaj*, [2] Laxmikant B. Marewad*, [3]Dr.Padmaja S. Giram, [4]Mr. Mahesh B. Manke,

[5]Dr. Shivakumar S. Ladde

[1,2]M.Pharma 2nd Yr. Student, [3]HOD of Pharmacology Dept., [4]Assistant Professor, [5]HOD of Pharmacy Practice Dept.
[1]Department of Pharmacology,
[1]Channabaseweshwar Pharmacy College (Degree), Latur, Maharashtra, India.

Abstract: Chronopharmacology is basically the study of the relationship between our internal biological rhythms and drugs. Essentially, this article is information for biologists, clinicians, pharmacists, and other professionals on the importance of circadian rhythms, chronotherapy, and chronopharmacology to human health. It also motivates researchers to develop new tools for the treatment of cardiovascular diseases such as arrhythmia and myocardial infarction. Cardiovascular disease stands as a top contributor to global mortality. Regulation and pathophysiological events of cardiovascular diseases are distributed over 24 h cycle.so, the new approaches of chronopharmacology can be use as perfect therapeutic tool for the management of the cardiovascular diseases and improve the mortality and morbidity rates. These approaches involve minimum risk and errors than any other homeostatic approach .so, the article is mainly focuses on chronopharmacological principles which are used as therapy of various cardiovascular diseases.

Keywords **- Chrono pharmacology, chronotherapy, cardiovascular disease, circadian rhythm.**

I. INTRODUCTION

Chronopharmacology involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics. The goal of chronopharmacology is to optimize the therapeutic effect and control or reduce the adverse effects without altering the functioning of the drug in the body. The onset and symptoms of diseases such as coronary infarction, angina pectoris, stroke and ventricular tachycardia are circadian phase dependent [1]. Cardiovascular functions like heart rate or blood pressure can show 24 h variation. Most of the CVS diseases can induce fatal and severe conditions or outcome. Cardiovascular functions in animal and man exhibit pronounced circadian temporal dependencies. Circadian patterns are not limited to global physiological functions (blood pressure, heart rate, blood flow, blood volume, ECG, etc.) But can be tracked down to the cellular and subcellular level of the sympathetic nervous system [2]. Clinical reports also document the circadian rhythms of cardiovascular disease incidence and symptoms, heart disease incidence, and mortality. Based on these physiological and pathophysiological findings, it is not surprising that the desired and adverse effects and pharmacokinetics of drugs used in cardiology exhibit a circadian time dependence [3].so, the goal is to improve our knowledge of periodic and predictable changes in both desired effects and tolerance of medication.

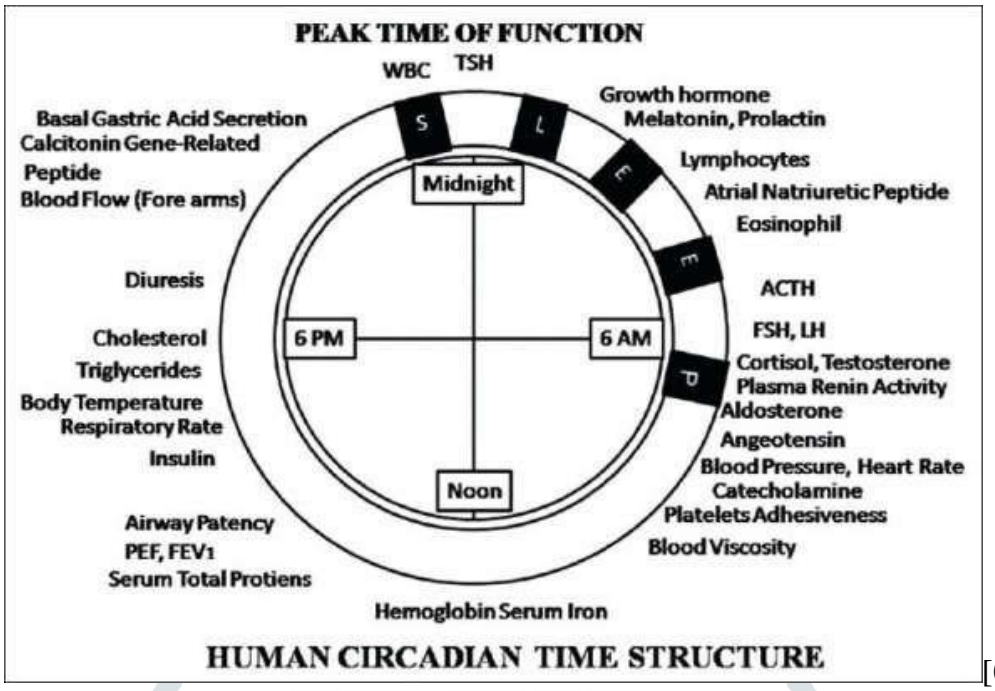
Chronobiology

It is the science that deals with the phenomenon of rhythm in living organisms. Derived from Chronos (time), bios (life) and logos (study), the term is an objective description of the structure of biological time and plays an important role in medicine. Aim of chronobiology is optimization of pharmacotherapeutics, taking into consideration rhythm dependencies in kinetics and dynamics of medications, predictable in time variability in the manifestation and severity of diseases.[4]

Circadian rhythm [5]

Mainly , circadian rhythm regulates the behavior, physiology and function of living organisms at many biochemical levels. It is defined as oscillations in the biological, physiological and behavioral function of an organism with a periodicity of 24 hrs. Now a days there are circadian variation in blood pressure and heart rates so many chances of occurrence of acute cardiovascular vascular diseases is the obvious thing.

Human circadian time structure



[6]

A circadian rhythm or circadian cycle, is a natural oscillation that repeats roughly every 24 hours.

Specific time that patient is taking the particular medicine is very important for the treatment success and the optimum clinical outcome is achieved. If symptoms of disease shown circadian variation there may be variation in drug release over time. Circadian rhythm based on sleep-activity cycle. Research field has demonstrated the importance of biological rhythms in drug therapy and this brought new approach to the development of drug delivery system which is with less risk ,error and adverse effect [6].

Pathogenesis of CVS according to circadian rhythm-

According to various studies the main cardiovascular disease events like myocardial infraction ,stroke and sudden death occur during morning nearly between 6am to 12 noon [1] . Increased secretion of cetacolamine leads to an increase in blood pressure in the morning, an increase in vascular tone and peripheral resistance in the morning, and a concomitant increase in heart rate in the morning or early afternoon.

Risk of heart attack appears mostly in early morning hours after awakening. For instance, capillary resistance and vascular reactivity are higher in the morning and decreases later in the day. Platelet aggregation increases and fibrinolytic activity dies down in the morning, resulting in a state of relative hypercoagulability of the blood. Blood pressure is lowest during sleep and rises early in the morning. Many anti-hypertensive drugs do not control the early morning blood pressure, when given once daily early in the morning.[4]

Therefore, many studies have shown that the pathophysiological events of cvs are not random. Cardiovascular function and its parameters exhibit circadian fluctuations like stroke volume ,blood flow cardiac output etc.

Various cardiovascular diseases

Chronopharmacology of hypertension

Hypertension, often referred to as high blood pressure, is a medical condition characterized by elevated blood pressure in the arteries, affecting 35% human adults. Tadei et al. (2018) stated that hypertension results from dysregulation of various homeostatic systems and progressive organ damage that affect normotension, leading to hypertension [7]

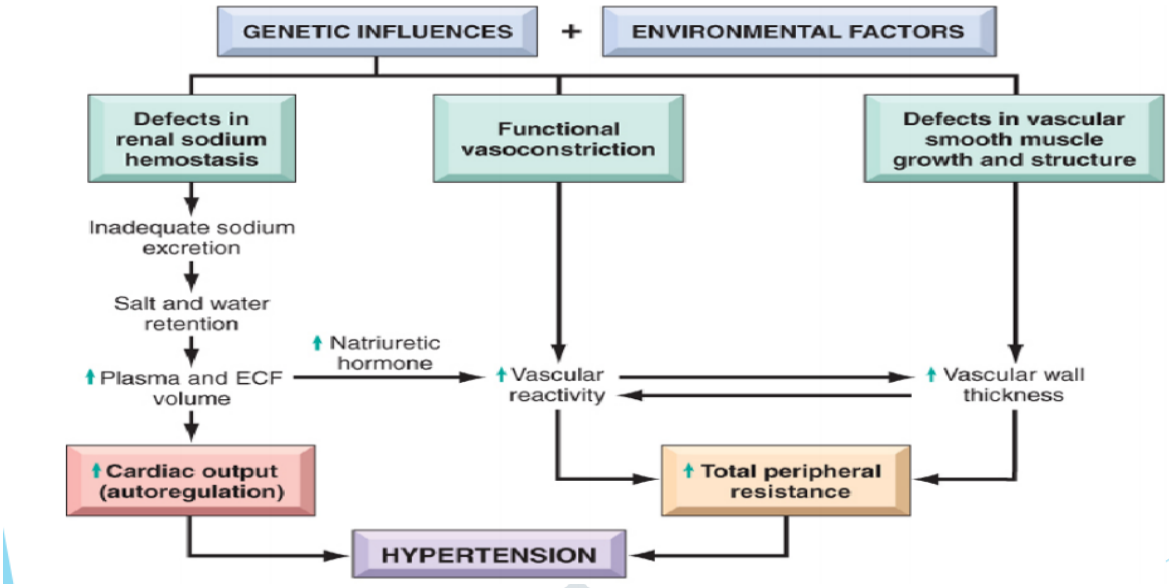


fig 1. Pathophysiology of hypertension (Chisolm, 2017, p. 15).

Blood pressure shows the 24h variation. also it is affected by many of the external factor like meal ,physical activity or emotional state etc. Circadian rhythms play an important role in regulating blood pressure, and considering these rhythms in the administration of antihypertensive drugs may enhance their efficacy.

Chronopharmacology of medication –

The goal of chronotherapy is to achieve maximum drug effect concentrations are synchronized with intrinsic circadian rhythms the process of disease or symptoms whereby increased efficacy and reduce adverse effects of treatment [9] . Research shows a majority of hypertensive patients taking antihypertensive medicine in the morning; some figures are as high as 80% that hypertensive patients taking all antihypertensive drugs the morning [10] . Medication treatments for high blood pressure include a variety of type of drug, such as diuretics, beta- and alpha-adrenoceptor blockers, calcium channels blockers, invertase w2wwinhibitors, at1 receptor blockers, etc. There are some medicines mentioned below with their dosage and timing.

Medication	Dosage (mg per day)	Treatment times	Comparison of morning vs. Evening dosing
Valsartan	160	Awakening bedtime	Significant reduction in asleep sbp/dbp with evening dosing
Olmesartan	20	Awakening bedtime	Significant reduction in asleep sbp/dbp with evening dosing
Telmisartan	80	Awakening bedtime	Significant reduction in asleep sbp/dbp with evening dosing
Lisinopril	20	08:00; 16:00; 22:00	Significant reduction in early morning sbp/dbp with evening dosing
Trandolapril	1	Awakening bedtime	Significant reduction in 24-h bp mean with evening dosing
Ramipril	5	Awakening bedtime	Significant reduction in 48-h sbp/dbp mean with evening dosing
Spirapril	6	Awakening bedtime	Significant reduction in asleep sbp/dbp with evening dosing
Nifedipine	30	Awakening bedtime	Significant reduction in 48-h sbp/dbp mean with evening dosing
torasemide	5	Awakening bedtime	Significant reduction in 48-h sbp/dbp mean with evening dosing

[11,12,13,9]

Accordingly, we can consider following points in the chronopharmacology of hypertension –

Blood pressure naturally fluctuates during the day and night due to circadian rhythms. It generally follows a pattern of being high during the day and low at night. This change is influenced by factors such as sleep-wake cycles, physical activity and stress. Many people experience a sharp rise in their blood pressure when they wake up in the morning, known as a "morning surge"[14]. This increase is associated with an increased risk of cardiovascular events, including heart attack and stroke. Studies show that the timing of taking hypertensive medications can affect blood pressure control and cardiovascular disease outcomes. For example, taking certain classes of high blood pressure medications at bedtime can effectively reduce nighttime blood pressure and morning flare-ups. Chronotherapy relies on circadian rhythms to achieve the best therapeutic results and minimize side effects. Studies have explored the effect of timing antihypertensive medications to match the body's natural blood pressure fluctuations. Different classes of antihypertensive medications have varying effects on blood pressure at different times of the day. Some medications work better during certain times due to their mechanisms of action. For example, diuretics might be more effective when taken in the morning due to their impact on fluid balance.[15] currently ,one extended release per day antihypertensive drugs provide safe and reliable treatment. Effectively lowers blood pressure within 24 hours the interval of drug release but the static pattern is not adjusted for daily physiological blood pressure fluctuations. Current time therapeutic calcium channels blockers are commercially available for dosing certain cardiovascular diseases[16]. A prominent example of chronopharmacology in hypertension is the bedtime administration of certain antihypertensive drugs. In the "bedtime treatment of hypertension" (bhyt) approach, one or more antihypertensive drugs are taken at bedtime rather than in the morning[17]. This approach has been linked to better blood pressure control and reduced cardiovascular risk in some people. During nighttime sleep, blood pressure typically drops in a pattern known as "dipping." however, in some people with high blood pressure, this pattern of decline may be blunted or reversed, resulting in persistent high blood pressure levels during the night. This is associated with an increased risk of cardiovascular complications. Optimal timing of drug administration varies from person to person based on circadian rhythm, lifestyle, and other factors. It is important to take an individualized approach to the timing of medication. Although chronopharmacological approaches may benefit some individuals, it is important to note that they may not be appropriate or necessary for everyone with hypertension. The decision to adjust medication timing should be made in consultation with the healthcare provider, taking into account the patient's overall health, medication and individual characteristics.

In conclusion, the chronopharmacology of hypertension provides valuable information to optimize the treatment of hypertension through the strategic timing of antihypertensive drugs. The human body's natural circadian rhythms play an important role in regulating blood pressure, which is typically higher during the day and lower at night. This physiological pattern highlights the potential benefits of tailoring drug delivery to these fluctuations. Various studies have suggested that antihypertensive medications that coincide with periods of high blood pressure can control high blood pressure and reduce the risk of cardiovascular events. A morning dose may help reduce the morning rise in blood pressure, while an evening dose may contribute to nighttime blood pressure control, especially for certain drug classes.

Common onset time of cardiovascular system [18,4]

Disease	**Common onset time**
Atrial fibrillation	Morning/ night
Ventricular tachycardia/fibrillation	Morning
Acute coronary syndrome	Early morning
Pulmonary embolism	Early morning
Cerebral infraction	Morning
Subarachnoid haemorrhage	Day time

Acute myocardial infraction (AMI) / pulmonary embolism (PE)

Pulmonary thromboembolism (PTE) and acute myocardial infarction (AMI) may have similar symptoms, including acute dyspnea, chest pain, syncope, and palpitations. Physical examination is nonspecific and cannot reliably distinguish between these two diagnoses [19]. Mi causes irreversible damage to the myocardium due to lack of oxygen. Mi can cause impairment of diastolic and systolic function and predispose patients to arrhythmias. Moreover, mi can lead to many serious complications. The key is to reperfuse the heart to restore blood flow[20]

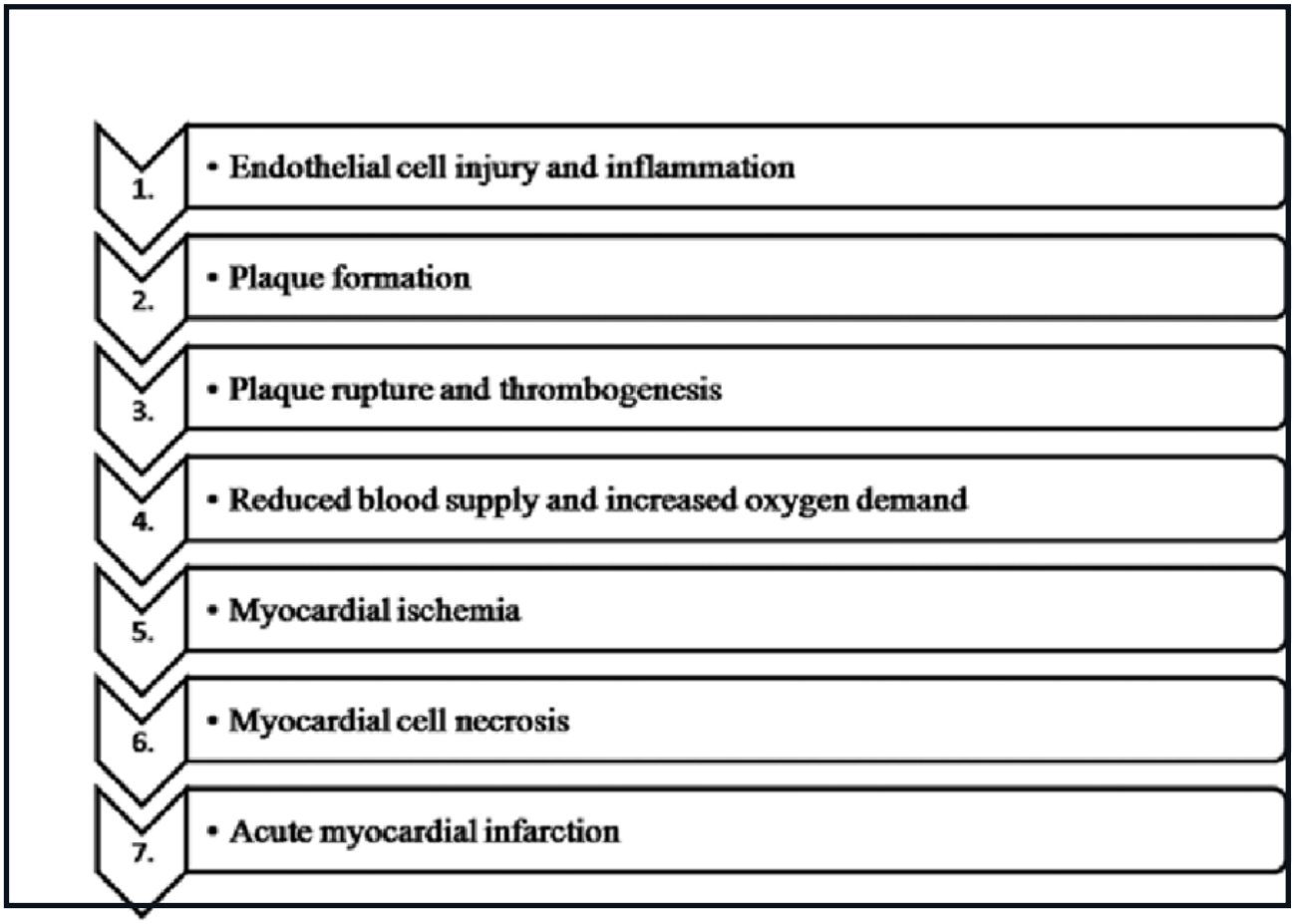


fig. 2 Pathophysiology of angina [21]

AMI and PE mainly occur during early morning. the systemic bp and oxygen demand is increased. Some studies suggest that autonomic nervous system plays important role in circadian pattern variation. A morning increase in the frequency of ischemic episodes is absent in diabetic patients with autonomic nervous dysfunction. Patients receiving beta-blocker do not show morning increase in the incidence of angina, ami & sudden death [1]. Platelets are not involved in the variation of AMI. Thromboembolic volume and aggregation activity has circadian oscillations. Invivo platelet catecholamine-induced activation secreted by the sympathetic nervous system circadian rhythm fashion. In addition platelet function and blood coagulation also increased in the morning [4]. However, related studies platelet activation does not show a distinct circadian pattern therefore, the expression of surface markers characteristic of platelet activation is unknown, that the internal clock system directly effects on circadian function of platelets [22].

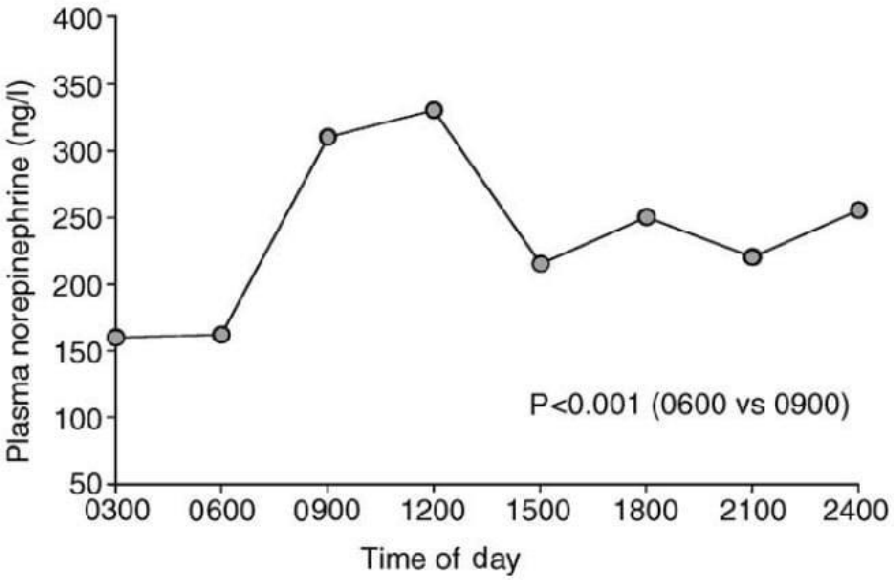


Fig. 3 Morning increases in the catecholamine hormone levels are greatest between 0600 and 0900 h and occur simultaneously with increases in platelet aggregability. [38]

We can consider following points in the chronopharmacology of AMI

Heart attacks often exhibit diurnal patterns, with a higher incidence occurring in the early morning hours. Thrombolytic (clot-dissolving) therapy is often used to treat acute myocardial infarction. The effectiveness of these medications might vary based on the time of administration. For example, research has suggested that administering thrombolytic therapy during the morning hours, when the risk of heart attack is higher, could enhance its benefits. After a heart attack, medications for secondary prevention, such as beta-blockers, ace inhibitors, and statins, are commonly prescribed. These medications often have different pharmacokinetic profiles that can influence their effectiveness and side effects. Tailoring the timing of these medications to coincide with the body's natural rhythms might optimize their benefits. Calcium channel blockers – mainly short-acting and non-delayed formulation—appears to be less effective than beta-adrenoceptor antagonists in reducing ischemia night and early morning activities (nifedipine – in contrast to atenolol – did not alter the circadian profiles of the episodes and the duration of ischemia) [23,24,25]

In conclusion its important to note that the field of chronopharmacology for myocardial infarction is complex and evolving. While there is evidence suggesting potential benefits of timing interventions and medications based on circadian rhythms, individual patient characteristics should always be considered.

Angina

Angina pectoris is one of the manifestations of acute coronary syndrome (acs) and can be further classified into stable angina and unstable angina. Stable angina is defined as having symptoms only during exertion. Unstable angina or symptoms that occur at rest require more prompt evaluation and management [26] the onset of angina pectoris and the frequency of angina attacks, both in stable angina and in vasospastic prinzmetal (variant) angina, exhibit a circadian rhythm, a finding which has been confirmed by many authors[27].

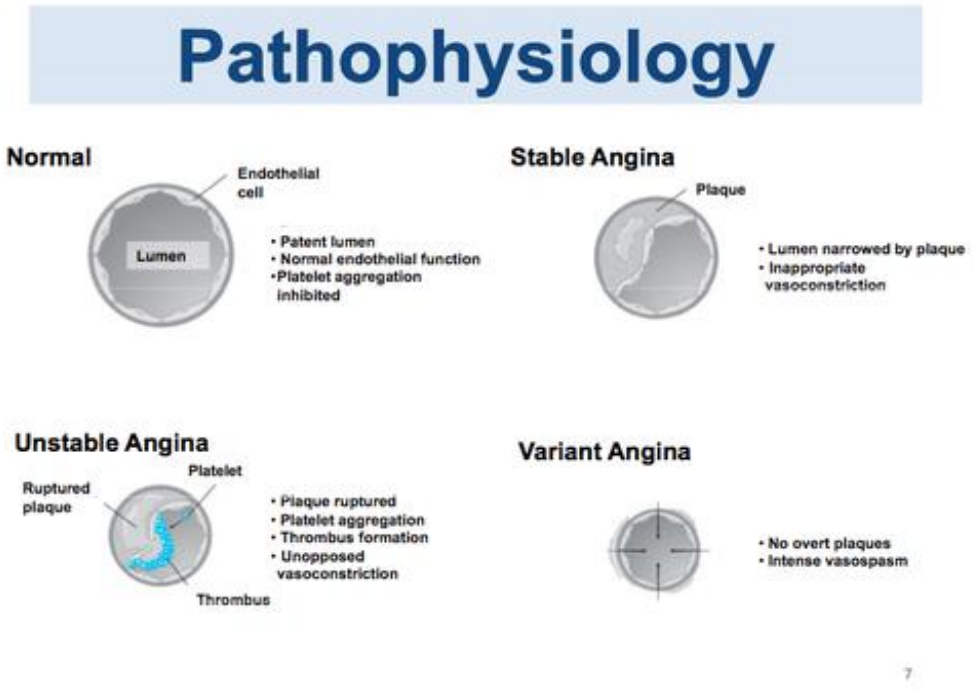


Fig. 3 angina [28]

The management of angina typically involves a combination of lifestyle modifications, such as dietary changes and exercise, as well as pharmacological interventions. Some commonly used drug classes for treating angina include nitrates, beta-blockers, calcium channel blockers, and antiplatelet agents. The administration timing of these drugs can influence their effectiveness and potential side effects. The antianginal drugs exert circadian phase dependent effects.

Preliminary evidence was provided by: the classic paper by yasue et al. (1979); this study included 13 patients with the prinzmetal(variant) angina, do the treadmill exercise test early in the morning (05:00-08:00) and then again. Afternoon (13:00 – 16:00). Exercise-induced angina attacks and electrocardiogram shows that all patients were abnormal in the morning, but only two patients were abnormal in the afternoon [29].

We can consider following points in the chronopharmacology of angina-

the timing of angina symptoms varies, and some people have more frequent symptoms at certain times of the day (such as early in the morning). Your medication regimen can be adjusted to ensure you are taking the most effective medication when your symptoms are most likely to occur. The absorption, distribution, metabolism, and excretion of drugs in the body can change throughout the day. This affects how quickly and how long the medicine works. Some drugs used to treat angina, such as nitrates and beta-blockers, may have different pharmacokinetic profiles depending on when they are administered. Interestingly, taking glyceryl trinitrate in the morning can prevent angina pectoris attacks and has a greater dilation effect on the coronary vessels than when administered in afternoon, indicating temporal changes in vasomotor tone [15]. Different classes of medications are used

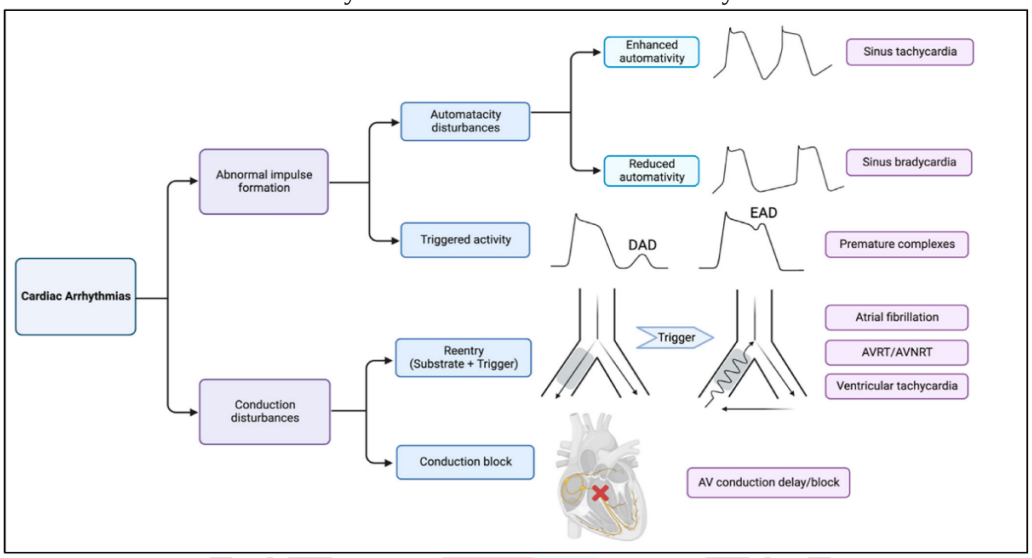
to treat angina, including nitrates, beta-blockers, calcium channel blockers, and others. Chronopharmacology could guide the selection and timing of these medications to ensure maximum benefit throughout the day.

In conclusion it's important for individuals with angina to follow their healthcare provider's recommendations regarding medication administration and timing. The choice of medication and its dosing schedule can vary based on the individual's specific condition, medical history, and the type of angina they have (stable angina, unstable angina, etc.). Always consult a healthcare professional for personalized medical advice and treatment plans.

Cardiac arrhythmia

Arrhythmia involves a wide range of disturbances in heart rate and rhythm abnormalities. Arrhythmias are broadly classified into bradyarrhythmia's and tachyarrhythmias based on heart rate. They are further classified according to origin, means of transmission, and associated syndromes[30]. An arrhythmia, or irregular heartbeat, is a problem with the rate or rhythm of your heartbeat [31].

Arrhythmia also follows the circadian rhythm



[32]

fig. summary of molecular mechanisms of arrhythmias.

Early studies repeatedly used 24-hour electrocardiogram (holter) monitoring to assess timing of frequent premature ventricular contractions (> 30 ectopic beats/hour) showing peak frequency between 0600 hours and noon [33,34].example can be, in retrospective study 68 patients who are documented as ventricular tachycardia [35], patients were interviewed about their heart attack symptoms such as palpitations, presyncope, and syncope. The peak occurrence time of ventricular tachycardia is at 0900 hours demonstrated however, chronobiologists criticism of these early reports that 24 hours is too short assessing the period of arrhythmia circadian patterns event [36,37] many studies clearly depict a trough of arrhythmogenesis during sleep - phenomenon known as 'sleep suppression', first described in the early 1970s by Dr. Lown [39]. The etiology of circadian patterns of ventricular arrhythmias may resemble to other conditions of cardiovascular events. Early morning surge in circulation of catecholamines can show occurrence of arrhythmias after awakening [40]. Other factors promote ventricular arrhythmias in patients with coronary heart disease illnesses include increased heart rate, blood pressure, and increased incidence of myocardial ischemia for the onset of cardiac arrhythmia paroxysmal atrial fibrillation is categorized into two types-[4]

1. Vagatonic paf- occurs at night.
2. Adrenergic paf- occurs during day time

We can consider following points in the chronopharmacology of arrhythmia-

The body's internal clock, known as the circadian rhythm, influences various physiological processes, including heart rate and rhythm. For instance, many arrhythmias, such as atrial fibrillation, exhibit diurnal variations, meaning they are more likely to occur at specific times of day. Chronotherapy aims to target medication administration during these vulnerable periods. Some arrhythmias can be triggered by factors like stress, physical activity, or sleep (ans functions) [1]. Chronotherapy takes into account the times of day when these triggers are more prevalent. For example, if stress-induced arrhythmias are more common in the morning, medications could be timed to provide protection during those hours. Some medications used to treat arrhythmias can prolong the qt interval, which is associated with an increased risk of certain arrhythmias. Administering these medications in the evening might be safer, as the risk of dangerous arrhythmias like torsades de pointes is higher during the night[41].

In conclusion the optimal timing of medication administration in the management of cardiac arrhythmias aims to provide the most effective control over heart rate and rhythm while minimizing the risk of adverse effects. However, individual patient factors, such as their specific arrhythmia type, overall health, and other medications being taken, also play a role in determining the appropriate timing and dosing regimen. Patients with cardiac arrhythmias should always follow their healthcare provider's recommendations regarding medication administration and timing.

II Conclusion

In conclusion, we can say the field of chronopharmacology in cardiovascular medicine provides valuable insights into optimal drug timing for cardiovascular disease management. This review article highlights the significant impact of circadian rhythms on various aspects of cardiovascular health, including blood pressure regulation, heart rate variability, and the occurrence of cardiovascular events. By carefully considering circadian variations in disease pathology and drug action, clinicians can tailor drug treatment regimens to match the body's natural rhythms, ultimately improving treatment outcomes and patient health. The emerging field of chronopharmacology in the context of cardiovascular disease holds great promise. By recognizing and exploiting the inherent rhythmic nature of cardiovascular physiology and pathology, clinicians can optimize the timing of interventions to improve outcomes and advance patient care in the field of cardiovascular health.

III. Reference

1) Maurya Krishna, B.C. Semwal, Singh Neelam, Khatoon Ruqsana, Paswan Shravan, Debjit Bhowmik. Chronopharmacology: As A Therapy for Cardiovascular Disease. Pharma Innovation 2012;1(3):06-15.

2) Baschieri F, Cortelli P. Circadian rhythms of cardiovascular autonomic function: Physiology and clinical implications in neurodegenerative diseases. Auton Neurosci. 2019 Mar;217:91-101. doi: 10.1016/j.autneu.2019.01.009. Epub 2019 Feb 1. PMID: 30744907.

3) Reddy S, Reddy V, Sharma S. Physiology, Circadian Rhythm. [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519507/

4) Ahmed Elsharkawy, Ahmed Ramadan, Mahmoud Abdo -Vital Role of Chronopharmacology in Cardiovascular Therapy January-February 2013:Vol 2:Issue 1 Journal of Scientific & Innovative Research (http://www.jsirjournal.com/Vol2Issue1016.pdf)

5) Farhud D, Aryan Z. Circadian Rhythm, Lifestyle and Health: A Narrative Review. Iran J Public Health. 2018 Aug;47(8):1068-1076. PMID: 30186777; PMCID: PMC6123576.

6) Akash Saini ,Pritee Gupta -CHRONOTHERAPEUTIC AGENTS: AN OVERVIEW -September 2017Indian Research Journal of Pharmacy and Science 4(3):1144-1152:

7) Taddei, S., Bruno, R. M., Masi, S., & Solini, A. (2018). Epidemiology and pathophysiology of hypertension.

8) Chisolm, O. E. (2017). Pathophysiology of hypertension and hypertension management. Web.

9)Chronopharmacology of high blood pressure—a critical review of clinical evidence -Potucek P. , Klimas J.

10) De La Sierra A, Redon J, Banegas JR, Segura J, Parati G, Gorostidi M, de la Cruz JJ, Sobrino J, Llisterri JL, Alonso J, Vinyoles E. Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. Hypertension. 2009 Mar 1;53(3):466-72.

11) Hermida RC, Ayala DE, Fernández JR, Portaluppi F, Fabbian F, Smolensky MH. Circadian rhythms in blood pressure regulation and optimization of hypertension treatment with ACE inhibitor and ARB medications. American journal of hypertension. 2011 Apr 1;24(4):383-91

12) Hermida RC, Ayala DE, Fontao MJ, Mojón A, Fernández JR. Chronotherapy with valsartan/amlodipine fixed combination: improved blood pressure control of essential hypertension with bedtime dosing. Chronobiology international. 2010 Jul 1;27(6):1287-303

13) Hermida RC, Ayala DE, Mojón A, Fernández JR. Chronotherapy with nifedipine GITS in hypertensive patients: improved efficacy and safety with bedtime dosing. American journal of hypertension.2008Aug1;21(8):948-54.

14) Morning blood pressure surge: pathophysiology, clinical relevance and therapeutic aspects Grzegorz Bilo, Andrea Grillo, Valentina Guida, and Gianfranco Parati , 2018; 11: 47–56.

15) Björn Lemmer (2007) Chronopharmacology of cardiovascular medications, Biological Rhythm Research, 38:3, 247-258, DOI: 10.1080/09291010600906216

16)Pandit V, Suresh S. Emerging role of biorhythms in optimizing treatment of disease. Indian. J novel drug delivery 2009; 1: 2-10

17)Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, Sineiro E, Castiñeira MC, Callejas PA, Pousa L, Salgado JL, Durán C, Sánchez JJ, Fernández JR, Mojón A, Ayala DE; Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J. 2020 Dec 21;41(48):4565-4576. doi: 10.1093/eurheartj/ehz754. PMID: 31641769.

18) Prisant LM, Chron obiology and chronotherapeutics- possible strategy for hypertension & ischemic h eart disease. Business briefing: North American pharmacotherapy 2004; 2:3 5.

19) Saida Zelfani, Hela Manai, Saoussen Laabidi, Abir Wahabi, Sara Akeri, and Mounir Daghfous - Pulmonary embolism mimicking acute myocardial infarction: a case report and review of literature Pan Afr Med J. 2019; 33: 275

20) Mechanic OJ, Gavin M, Grossman SA. Acute Myocardial Infarction. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan

21) Diagnostic markers of acute myocardial infarction (Review) -Narasimhan Malathi July 2015 Biomedical Reports 3(6)

22)Swapna V Deshpande and Vinita V Kale. Chronopharmacology and time controlled dosage forms. Indian J pharma Educ Res 2007;41(2):80- 86.

23) Lemmer B. 1996. Differential effects of antihypertensive drugs on circadian rhythm in blood pressure from the chronobiological point of view. Blood Press Monit 1:161 – 169.

24)Lemmer B, Portaluppi F. 1997. Chronopharmacology of cardiovascular diseases. In: Redfern P, Lemmer B, editors.

25) Lemmer B. 2006. The importance of circadian rhythms on drug response in hypertension and coronary heart disease – from mice and man. Pharmacol Ther 111:629 – 651.

26)Hermiz C, Sedhai YR. Angina. [Updated 2023 Jun 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557672/

27)Willich SN, Muller JE. 1996. Triggering of Acute Coronary Syndromes. Dordrecht: Kluwer Academic.

28)Pharmacologic Management of Angina Pectoris Flashcards | Quizlet
29)Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, Tanaka S. 1979. Circadian variation of exercise capacity in patients with Prinzmetal's variant angina: role of exercise-induced coronary arterial spasm. Circulation 59:938 –948.
30) Desai DS, Hajouli S. Arrhythmias. [Updated 2023 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558923/
31)What Is an Arrhythmia? | NHLBI, NIH -National Institutes of Health (.gov) (https://www.nhlbi.nih.gov › health › arrhythmias)
32) Wha Rhee ,Yingfeng Deng and Zhao V. Wang Mitochondrial Dysfunction in Cardiac Arrhythmias by Jielin Deng ,Yunqiu Jiang ,Zhen Bouman Chen ,June
33) Seigel D, Black DM, Seeley DG, Mulley SB. Circadian variation in ventricular arrhythmias in hypertensive men. Am J Cardiol 1992; 69:344–347.
34) Raeder EA, Hahnloser SH, Graboys TB, Padrid PS, Lampert S, Lown B. Spontaneous variability and circadian distribution of ectopic activity in patients with malignant ventricular arrhythmia. J. Am Coll Cardiol 1988; 12:656–661.
35) Cornelissen G, Bakkan E, Delmore P, Orth-Gomer K, Akerstedt T, Caradentre O, et al. From various kinds of heart rate variability to chronocardiology. Am J Cardiol 1990; 66:863–868.
36) Twidale N, Taylor S, Heddle WF, Gyres BF, Tonkin AM. Morning increase in the time of onset of sustained ventricular tachycardia. Am J Cardiol 1989; 64:1204–1206.
37) Wood MA, Simpson PM, London WB, Stambler BS, Herre JM, Bernstein RC, et al. Circadian pattern of ventricular tachyarrhythmias in patients with implantable cardioverter-defibrillators. J Am Coll Cardiol 1995; 25:901–907.
38) Tofler GH, Brezinski D, Schafer AI, Czeisler CA, Rutherford JD, Willich SN, et al. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 1987; 316: 1514–1518.
39) Lown B, Tykocinsky M, Garfein A, Brooks P. Sleep and ventricular premature beats. Circulation 1973; 48:691–701.
40) William B. White and Gina M. LaRocca -Chronopharmacology of cardiovascular therapy, Blood Pressure Monitoring 2002, 7:199-207
41)Cohagan B, Brandis D. Torsade de Pointes. [Updated 2023 Aug 8]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459388/