Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Review Article

The circadian based hypertension-management: new approach for better blood pressure goals

Muhammad Firdaus[1*], Cholid Tri Tjahjono[2]

[1] Brawijaya Cardiovascular Research Center, Faculty of Medicine Universitas Brawijaya, Malang, Indonesia
[2] Department of Cardiology and Vascular Medicine Faculty of Medicine Universitas Brawijaya - Dr. Saiful Anwar General Hospital, Malang, Indonesia

ARTICLE INFO

Keyword :
Ambulatory Blood Pressure Monitoring;
Blood Pressure;
Circardian Rhytm.

ABSTRACT

Hypertension, a primary changeable risk factor for overall mortality, affects approximately 1.4 billion people worldwide, accounting for about 31% of the global adult population. The primary method of diagnosis is through in-office or clinic blood pressure readings, which do not consider the circadian rhythm's fluctuations. Various homeostatic parameters, including blood pressure, are influenced by circadian rhythms, which follow a day-night cycle. Blood pressure typically decreases at night and rises during the day in line with the circadian rhythm. 24-hour ambulatory blood pressure monitoring offers a more comprehensive evaluation of hypertension. The phenomena of nocturnal blood pressure and the dipping pattern are closely interconnected characteristics that provide comparable therapeutic insights. In hypertensive patients, nighttime blood pressures were found to be a better predictor of cardiovascular and all-cause mortality outcomes than daytime systolic pressures. The current range of anti-hypertensive medications used to manage hypertension reveals that while some have an impact on circadian rhythms, others do not. Existing research on these drugs presents mixed views on the benefits of administering hypertension medication in the morning versus the evening. A significant study, known as the BedMed trial, is currently in progress to assess the cardiovascular effects of administering hypertension medication at bedtime as opposed to the traditional morning administration. This study could potentially provide valuable insights for improved future management of hypertension.

1. Introduction

Hypertension, a primary changeable risk factor for overall mortality, affects approximately 1.4 billion people worldwide, Approximately 31% of the worldwide adult population is represented. The primary method of diagnosis is through in-office or clinic blood pressure readings, which do not consider the circadian rhythm's fluctuations. Circadian rhythms are 24-hour cycles that play a crucial role in coordinating many physiological functions, including blood pressure regulation. The diurnal blood pressure pattern is characterized by an initial increase upon awakening, a stable level throughout the day, and a subsequent decrease during the night (resulting in a reduction of 10%–20% from the average daytime blood pressure). Circadian rhythms exert an impact on the pathophysiology of the cardiovascular system, resulting in the manifestation of symptoms and occurrence of life-threatening or fatal events in a 24-hour pattern, a phenomenon known as chronopathology. Additionally, circadian rhythms influence the pharmacokinetics and pharmacodynamics of medications, giving rise to variations in their effectiveness and safety depending on the time of administration. This field of study is referred to as chronopharmacology. Ambulatory blood pressure monitoring (ABPM) is a commonly used method to detect blood pressure levels based on the circadian rhythm. To accomplish this, a portable digital gadget is connected to a blood pressure cuff, which collects measurements at regular intervals over a period of 24 hours..[1,2]

The pharmacokinetics of antihypertensive drugs are substantially impacted by circadian rhythms, encompassing processes such as absorption, distribution, metabolism, and elimination. Moreover, the pharmacokinetics of these pharmaceutical compounds and the underlying biological mechanism governing the 24-hour blood pressure fluctuations are influenced by variations in the timing of medication administration and the natural circadian rhythms. However, existing guidelines for hypertension management do not include specific recommendations for the most optimal timing for the administration of medications. However, most healthcare professionals conventionally advise hypertensive patients to take their blood pressure-lowering therapy in the morning at the start of their active period. This guideline may derive from large-scale epidemiological research demonstrating that occurrences such as angina pectoris, myocardial infarction, sudden cardiac death, and hemorrhagic and ischemic stroke most frequently occur during the early hours of the daily activity period.[3]

* Corresponding author at: Brawijaya Cardiovascular Research Center, Faculty of Medicine Universitas Brawijaya, Malang, Indonesia
E-mail address: muhfirdaus.dr@gmail.com (M. Firdaus).

https://doi.org/10.21776.ub.hsj.2024.005.04.2
Received 17 October 2023; Received in revised form 9 November 2023; Accepted 20 November 2023.
Available online 28 October 2024

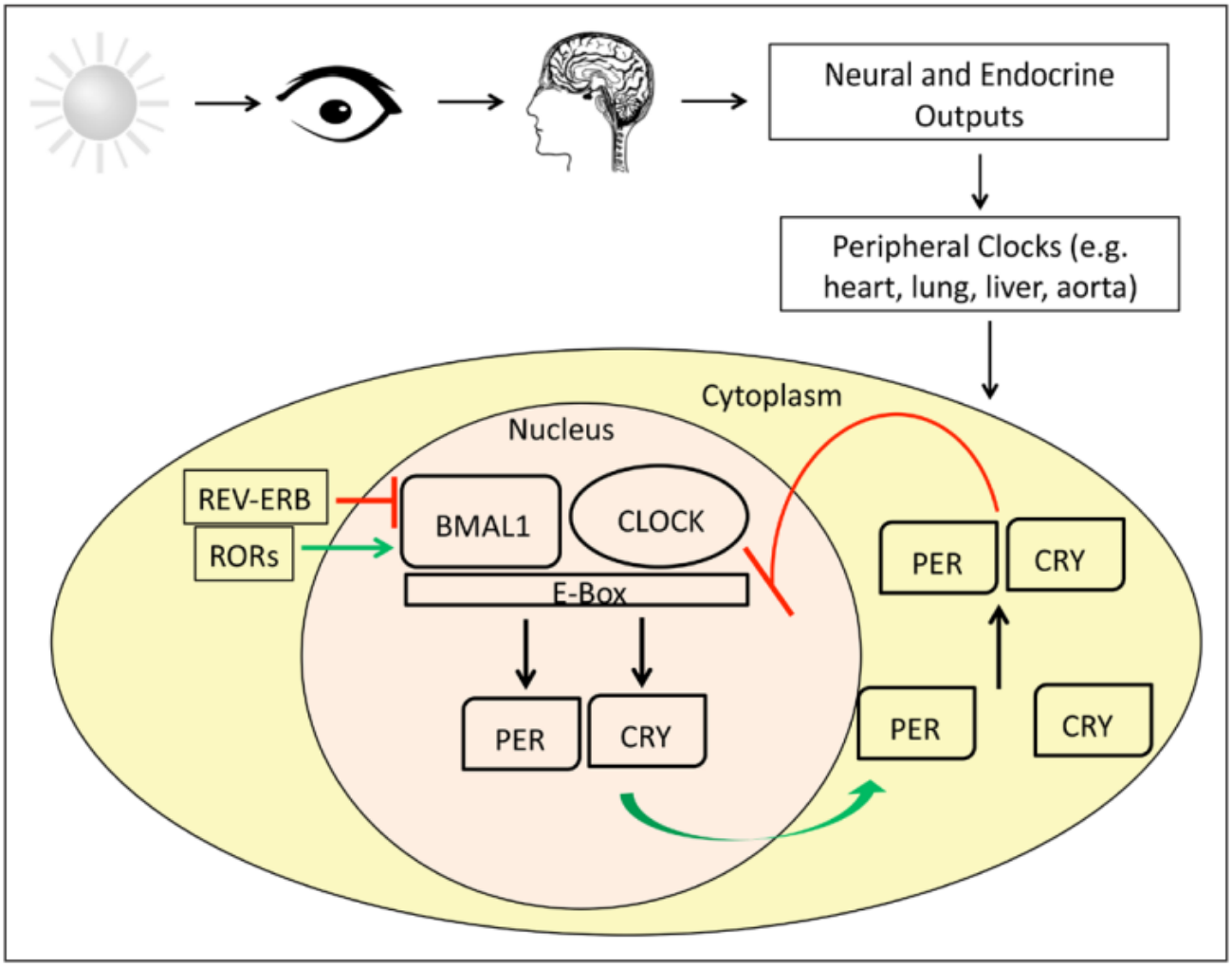

Figure 1. Constituents of the circadian clock at the molecular level. The mammalian circadian system is initiated by light signals that are absorbed by photoreceptors situated in the eyes and subsequently conveyed to the suprachiasmatic nucleus. The circadian system's molecular composition consists of transcriptional feedback loops initiated by the circadian genes CLOCK and BMAL1. When activated, these genes form heterodimers in the nucleus and bind to E-box DNA elements on target gene promoters. Subsequently, the PERIOD genes (Per1 and Per2) and CRYPTOCHROME genes (Cry1 and Cry2) are activated. The PER and CRY proteins form a complex in the cytoplasm and prevent the CLOCK:BMAL1 dimers from carrying out their transcriptional activity. The process of heterodimerization between CLOCK and BMAL1 also triggers the transcription of the orphan nuclear-receptor genes Rev-Erbα/β and RORα/β. ROR proteins have the ability to stimulate the transcription of BMAL1, while REV-Erb has the ability to inhibit it. BMAL1 is an abbreviation for brain and muscle Arnt-like protein-1.[4]

The objective of this study is to provide a comprehensive summary of recent advancements in research and clinical applications pertaining to the relationship between circadian rhythms and hypertension. Furthermore, we emphasize the impact of circadian rhythms on blood pressure and its relationship to hypertension. We also discuss the potential future implications of this significant discovery.

2. Circadian Rhytm in General

Biological activities and functions exhibit rhythmic oscillations over time. The regulation of circadian rhythms, which have significant implications for daily activities and medical practice, is governed by an inherent central control system located in the paired suprachiasmatic nuclei (SCN) of the hypothalamus. The central time-keeping mechanism consists of the SCN clock genes Per1, Per2, Per3, Bmal, Clock, and Cry, as well as their gene products, which are involved in rhythmic activity. The biological system for measuring time also encompasses several peripheral cell, tissue, and organ clocks that follow a daily rhythm and are controlled and synchronized by the central master clock known as the SCN. The central and peripheral circadian clocks regulate the body's circadian time structure (CTS) through the activation of clock-controlled genes. This CTS is synchronized with environmental time cues to optimize human metabolic and performance efficiency during the day and promote repair and rejuvenation during nighttime rest/sleep.[4,5]

Beyond the molecular level, the circadian rhythms of cardiovascular physiology and function are widely recognized. Additionally, there is a distinct pattern of circadian rhythmicity in the pathological processes that contribute to the 24-hour timing of severe and fatal cardiovascular disease events. There is now strong and convincing evidence that the daily 12-hour light and 12-hour dark cycle has a significant impact on the physiology and pathology of the cardiovascular system (Figure 2). An important observation is that the circadian rhythm has a significant impact on cardiovascular function, particularly on blood pressure (BP) and heart rate (HR). The parameters display diurnal rhythmicity, with blood pressure being higher in the morning and lower in the evening. Many cardiovascular diseases (CVDs) and cardiac events, such as myocardial infarction (MI), arrhythmias, stroke, heart failure, and sudden cardiac death, show a diurnal pattern with a higher occurrence of occurrences in the early morning. Additionally, the timing of administration of different types of drugs used to control cardiovascular disease (CVD) risk can significantly affect their pharmacokinetics (PK) and pharmacodynamics (PD), especially in relation to the regulation of circadian rhythms. Therefore, it is crucial to customize preventive and therapeutic interventions based on the factors that determine circadian rhythm in order to maximize desired results.[4,5]

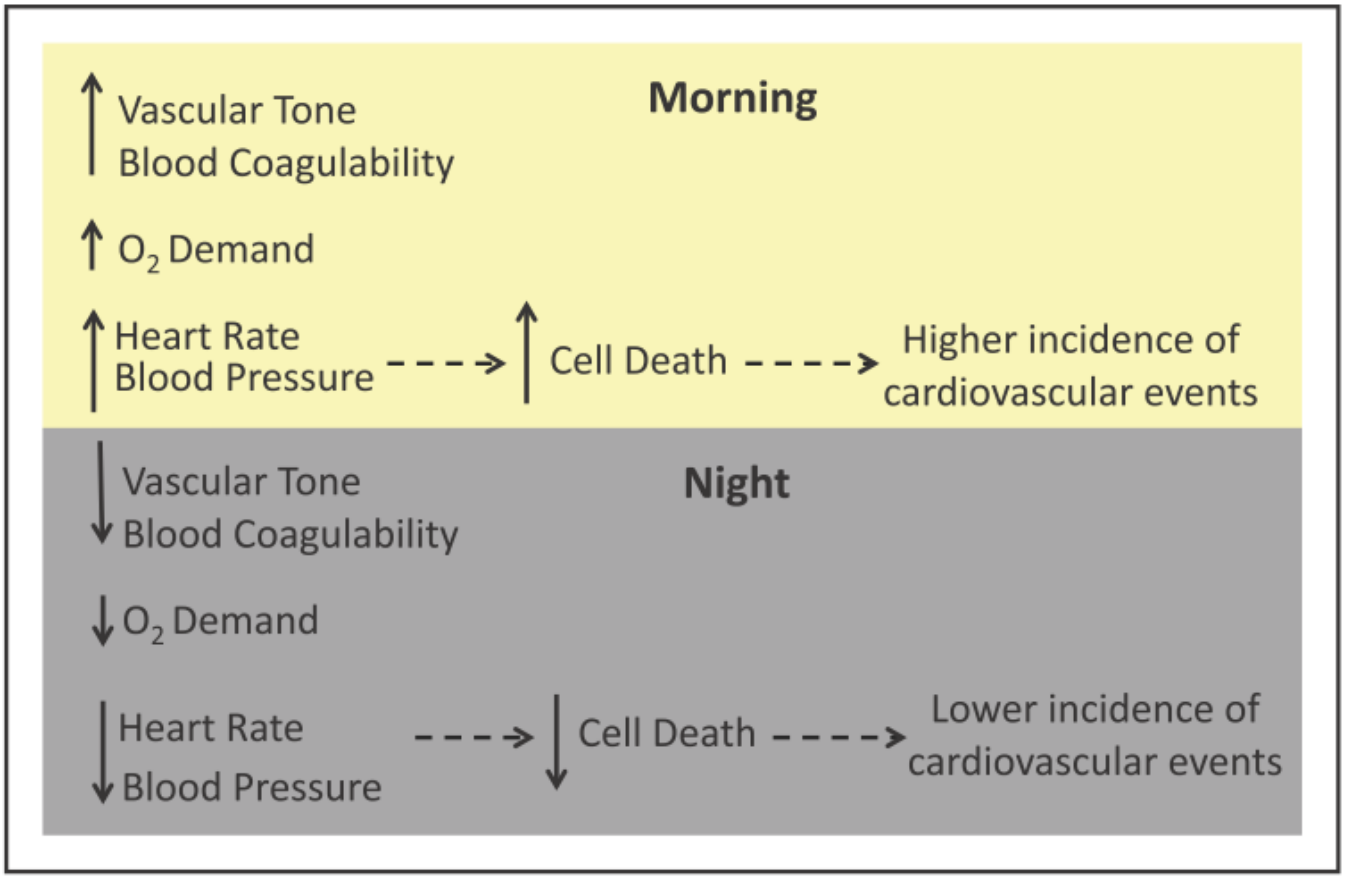

Figure 2. The circadian rhythm regulates the physiological and pathological activities of the heart. During the nocturnal period, there is a decrease in vascular tone and blood coagulability. These effects are accompanied with a decrease in heart rate and blood pressure, as well as a decrease in cell death. Collectively, it results in a reduced occurrence of cardiovascular events. During the morning hours, there is an elevation in vascular tone and blood coagulability. This is accompanied by an increase in oxygen demand, heart rate, and blood pressure, as well as the initiation of cellular apoptosis. The convergence of these mechanisms culminates in heightened occurrence of cardiovascular events.[4]

3. 24-hour ABPM as One of The Examination Methods Recommended for The Management of Hypertensive Patients

Traditionally, blood pressure (BP) has been monitored in a clinical environment. However, there's a growing interest in tracking BP outside of this setting. Ambulatory Blood Pressure Monitoring (ABPM) records a patient's BP at intervals of 15-30 minutes during the day and 30-60 minutes while they sleep, offering a more comprehensive understanding of hypertension. Research has consistently shown that ABPM is a better predictor of health outcomes than conventional office measurements. Ambulatory Blood Pressure Monitoring (ABPM) is often regarded as the most reliable and accurate method for measuring blood pressure as it outperforms both clinic and home BP measurements in diagnosing hypertension.ABPM also provides valuable information that cannot be obtained through other BP measurement methods, such as 24-hour BP, BP variability, nocturnal "dipping status," and morning BP surge. Moreover, ambulatory blood pressure monitoring (ABPM) measurements provide an assessment of an individual's blood pressure during their usual everyday context, allowing for the evaluation of the influence of environmental and emotional factors on blood pressure.[6,7]

The introduction of ambulatory blood pressure monitoring initiated the search for novel and clinically significant patterns that may be identified through the observation of blood pressure fluctuations over a 24-hour period. This instrument provided healthcare professionals with the capability to analyze the circadian variation in blood pressure. Various methodologies have been employed to examine the diurnal fluctuations in blood pressure, including categorizing hypertension according to measurements obtained during both daytime and overnight periods, evaluating the shift in blood pressure levels from daytime to evening, and delineating the phenomenon known as the "morning surge" in blood pressure.[6]

The current guidelines advocate for the adoption of out-of-office blood pressure (BP) monitoring, namely Ambulatory Blood Pressure Monitoring (ABPM), as a means to assist in the identification of hypertension. This encompasses the process of identifying and verifying the presence of white-coat hypertension and masked hypertension. The determination of hypertension using ambulatory blood pressure monitoring (ABPM) should be set according to the subsequent thresholds: An individual is considered to have sustained hypertension when their average 24-hour blood pressure (BP) is equal to or greater than 130/80 mmHg. Daytime hypertension is indicated by an average daytime BP of equal to or greater than 135/85 mmHg. Nocturnal hypertension is characterized by an average nighttime BP of equal to or greater than 120/70 mmHg. Morning hypertension is identified by an average morning BP of equal to or greater than 135/85 mmHg.[8]

The parameter of Ambulatory Blood Pressure Monitoring (ABPM) that may exhibit the highest level of consistency and reliability for risk categorization is nocturnal blood pressure (BP). The potential indication of co-occurring disorders, such as Obstructive Sleep Apnea (OSA), may be inferred from the occurrence of nocturnal hypertension, defined as blood pressure equal to or exceeding 120/70 mmHg. Furthermore, an elevated nocturnal blood pressure (BP) trend has been associated with a particularly adverse prognosis in terms of the occurrence of cardiac events and stroke. Elderly hypertension patients with a severe dipper pattern appear to have an increased susceptibility to stroke.

Table 1. Indications for Ambulatory Blood Pressure Monitoring in Clinical Practice.[9]

Objective	Clinical Indication
To diagnose white-coat hypertension	Stage-1 office hypertension;
	High variability of office blood pressure;
	To exclude pseudo-resistant hypertension;
	Severely elevated office blood pressure without signs of target organ damage.
To diagnose masked hypertension	Elevated blood pressure (120-129/80 mmHg) or a high-normal office blood pressure (130-139/85-89 mmHg) according to ACC/AHA and ESC/ESH guidelines, respectively;
	Normal office blood pressure with signs of target organ damage;
	Normal office blood pressure in high-risk patients;
	Risk factors for masked hypertension, ie, diabetes, overweight and obesity, excessive alcohol intake, smoking, etc.
To evaluate blood pressure during the day in untreated or treated patients	To assess blood pressure control during the whole day in patients on antihypertensive drug treatment;
	Suspicion of orthostatic or treatment-induces hypertension;
	Suspicion of nocturnal hypertension, such as in sleep apnea, chronic kidney disease, autonomic dysfunction, diabetes, endocrine hypertension, etc.

The morning blood pressure spike is an important factor in blood pressure variability. It is characterized by the disparity between the lowest blood pressure recorded at midnight and the blood pressure measured two hours after waking up. There exists a positive correlation between experiencing a jump in blood pressure during the early morning hours and an increased likelihood of encountering adverse cardiovascular and cerebrovascular events, with a specific emphasis on the occurrence of hemorrhagic stroke.[8]

4. Dipper, Nocturnal BP as a Form of Circadian Rhythm in The CV System and Its Clinical Significance in Hypertensive Patients

According to the 2017 guidelines of the American College of Cardiology/American Heart Association, nocturnal hypertension is defined as a condition where blood pressure during the midnight hours exceeds 110/65 mmHg. In general, blood pressure patterns tend to demonstrate a decline during the sleep period, a phenomenon that can be largely ascribed to reduced physical activity and sleep-wake behavioral patterns. The circadian rhythm is influenced by both the inherent rhythm of central and peripheral clock genes, which play a role in regulating neurohormonal factors and cardiovascular systems. The circadian rhythm patterns of blood pressure have been classified into different categories. Individuals who have a decrease in systolic blood pressure ranging from 10% to 20% during the overnight in comparison to daylight are commonly referred to as "dippers." On the other hand, those who exhibit a nocturnal decline in blood pressure above 20% are classified as "extreme dippers." Individuals who have a reduction in blood pressure of less than 10% during nocturnal hours are sometimes referred to as "non-dippers." Another form of this condition is known as reverse dipping, wherein the average blood pressure during nighttime exceeds the average blood pressure during daylight.[6]

Patients with secondary hypertension, severe refractory hypertension, pregnancy, type 1 and 2 diabetes mellitus, sleep apnea syndrome, and autonomic dysfunction often exhibit nocturnal hypertension. The exact etiology of the reduced nocturnal blood pressure (BP) dip remains uncertain; however, there is speculation that impaired renal salt excretion may be a contributing factor. In the context of impaired renal function, diurnal sodium excretion may be diminished, so potentially triggering the pressure natriuresis mechanism during nocturnal hours as a compensatory response to enhance sodium excretion, consequently leading to higher nocturnal blood pressure. As a result, individuals with chronic kidney disease (CKD) frequently have elevated blood pressure during overnight hours. There are several physiological reasons that could potentially lead to elevated blood pressure during overnight hours. These aspects include heightened sympathetic tone, reduced baroreceptor sensitivity, and impaired vascular compliance.[10,11]

Nocturnal BP and the dipping pattern are two connected aspects that offer similar clinical information. Individuals diagnosed with nocturnal hypertension can be classified into two categories: dippers and non-dippers. Based on the available data, it is expected that individuals who display both nocturnal hypertension and an absence of nocturnal blood pressure decline will possess the most pronounced cardiovascular risk profile. Hence, the utilization of both overnight blood pressure levels and dipping profiles provides complementary insights into the evaluation of cardiovascular risk among individuals with hypertension. The presence of nocturnal hypertension carries substantial consequences for the development of left ventricular hypertrophy (LVH). The present study utilized a comprehensive longitudinal design using a sizable population sample to investigate the association between elevated nighttime systolic blood pressure and the occurrence of left ventricular hypertrophy. Multiple studies have also provided evidence of a robust correlation between nocturnal blood pressure and clinical outcomes. In a recent study conducted on a population-based cohort, it was observed that individuals with non-dipping and reverse dipping blood pressure exhibited significantly elevated rates of cardiovascular events and mortality. These associations remained significant even after accounting for variations in 24-hour blood pressure levels by appropriate adjustments. The findings of a comprehensive analysis indicate that nocturnal blood pressures had a higher predictive value for cardiovascular and all-cause death outcomes compared to systolic daytime pressures in both hypertensive individuals and random people from Asian, European, and South American populations. In a longitudinal study involving a sample size of 13,844 individuals diagnosed with hypertension, residing in 9 distinct areas, the inclusion of adjustments for clinic, daytime, and nighttime systolic blood pressure yielded sustained predictive significance for nocturnal systolic BP. Conversely, clinic and daytime systolic BPs exhibited a complete loss of their prognostic value. Thus, evening blood pressures could potentially provide critical prognostic information in hypertension patients.[6,12,13]

The precise mechanism underlying the greater predictive value of nighttime blood pressure as a biomarker for cardiovascular risk in comparison to daytime BP remains uncertain. Nocturnal blood pressure measures are conducted in a more controlled environment, adhering to regulated protocols, and are less susceptible to the influence of environmental factors that are known to contribute to fluctuations in BP. Nevertheless, the process of detecting nocturnal blood pressure poses various obstacles. The variability of sleep quality on a nightly basis has a substantial influence on nocturnal blood pressure. The frequency of measurements is often constrained to two per hour, as opposed to the higher frequency of three or four measurements per hour observed during daylight hours. Moreover, the differentiation between periods of sleep and weakfulness in the

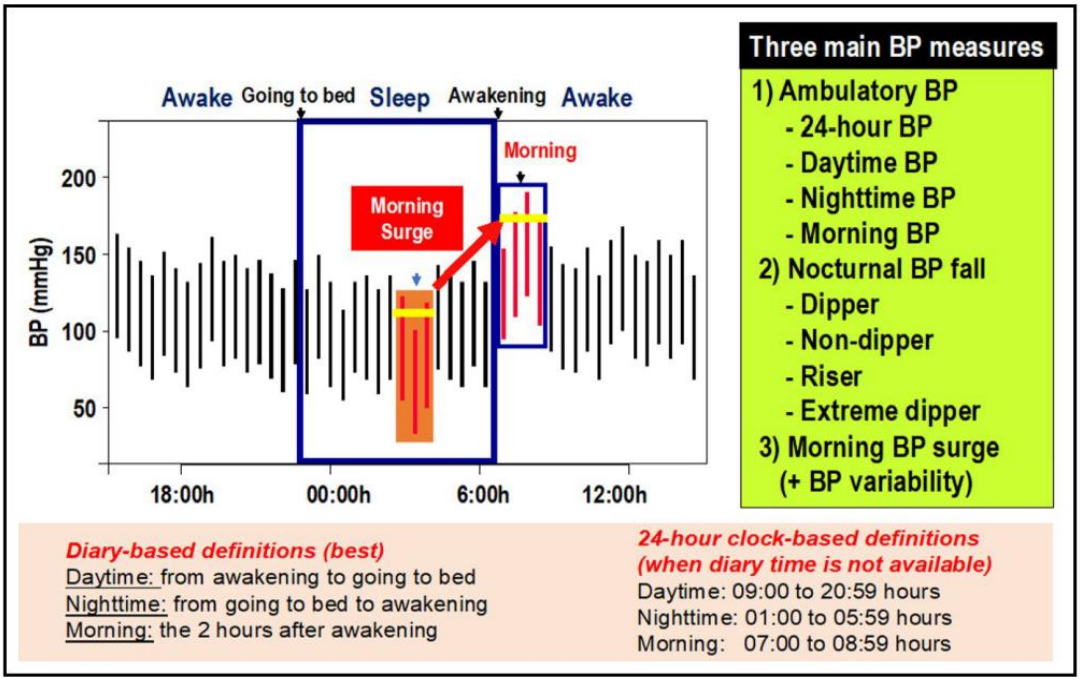

Figure 1. Blood pressure measures determined using ambulatory blood pressure monitoring. The clock-based definition of daytime, nighttime, and morning is as follows: daytime is from the moment of awakening until going to bed, nighttime is from going to bed until awakening, and dawn refers to the 2 hours following awakening.[7]

context of ABPM is sometimes lacking precision unless a rigorous procedure is adhered to. Finally, it is worth noting that a previous study found no significant impact of automatic cuff inflations on overnight intraarterial blood pressure. However, it is important to acknowledge that a considerable number of patients have reported experiencing sleep problems while doing ABPM.[13]

5. Morning BP and Morning Surge as Manifestations of Circadian Rhythms in the CV System and Clinical Significance in Hypertensive Patients

The morning surge in blood pressure is a well-established physiological phenomenon characterized by circadian or diurnal variations in BP. The term "morning blood pressure" refers to the blood pressure measurement taken two hours after awakening, while the "lowest nighttime blood pressure" refers to the lowest blood pressure recorded during the midnight period. The morning blood pressure is calculated by subtracting the lowest nighttime blood pressure from it. The regulation of the circadian rhythm of normal blood pressure is governed by a multitude of neurohumoral variables. The activation of the sympathetic autonomic nervous system and the suppression of vagal tone result in a rise in BP upon awakening. Concurrently, many hemodynamic measures, such as heart rate, vasomotor tone, and blood viscosity, also exhibit an increase. Several factors, including notably increased levels of adrenaline in the bloodstream, sympathetic neuronal reflexes associated to posture, and the release of renin and angiotensin II in the early morning, may together contribute to the occurrence of morning surges. The greatest determinant of increased blood pressure during waking is physical activity conducted throughout the daytime. There are several more elements that contribute to the fluctuation of blood pressure. These factors include hereditary factors, mechanical forces that occur during ventilation, local vasomotor phenomena, neurohumoral factors, artery wall thickness, baroreflex mechanisms, and seasonal variations in body temperature. An elevated morning surge has the potential to result in adverse effects on target organs, including left ventricular hypertrophy and left ventricular mass index, arterial stiffness and carotid atherosclerosis, as well as renal albuminuria. Moreover, there is a correlation between an amplified Early Morning Blood Pressure Surge (EMBS) and various negative cardiovascular and cerebrovascular occurrences, specifically hemorrhagic stroke.[12]

6. Consumption of Circadian Rhythm-Based Anti-Hypertension Drugs As An Alternative to Achieve Successful Control of Hypertension Therapy

The pharmacological treatment of hypertension involves various classes of antihypertensive medications, including angiotensin II receptor blockers, diuretics, calcium channel blockers, α-and β-adrenoceptor antagonists, angiotensin-converting enzyme inhibitors, among others. These medications have different sites or mechanisms of action, but the primary mechanisms that regulate blood pressure are dependent on the circadian phase. The most common treatment strategy for antihypertensive drugs is once-daily administration (typically in the morning), likely adopted to enhance patient adherence and compliance. Understanding physiological rhythms and their alterations can help improve the medical management of hypertension in terms of both medication efficacy and tolerability.[13,14]

The ability to maintain blood pressure within normal range during a 24-hour period depends on the pharmacodynamic and pharmacokinetic characteristics of antihypertensive medications. The pharmacokinetics of these medications following oral administration are also affected by diurnal fluctuations in gastrointestinal function, transport mechanisms, and enzymatic pathways involved in drug metabolism. In comparison to long-acting medications, short-acting pharmaceuticals are less likely to provide continuous coverage over a 24-hour period and necessitate multiple daily administrations. It is worth mentioning that a considerable number of antihypertensive medications that are advertised as being effective for a full day do not provide continuous coverage over the entire 24-hour period, and their effectiveness diminishes in the latter hours of the prescribed dosing interval. There may also be a dissociation between a drug's ability to lower BP for 24 hours and its ability to give organ protection for the same period, as shown with blockers of the renin-angiotensin system.[13]

The effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on blood pressure readings vary depending on the timing of administration, which is controlled by the circadian activities of renin and aldosterone. Indeed, the administration of ramipril, enalapril, zofenopril, benazepril, and perindopril in the evening elicits a more pronounced decrease in nocturnal blood pressure, afterwards followed by a slower rise during daytime hours. The administration of ACE-inhibitors in the evening has been shown to reduce blood pressure readings during the night time, resulting in a notable alteration of the circadian pattern of blood pressure towards a more natural profile. Several research have yielded comparable findings when examining the impacts of angiotensin receptor blockers (ARBs). The administration of ARBs at bedtime demonstrated a stabilization of the circadian blood pressure profile, resulting in a shift towards a more physiological rhythm. These medications exert an impact on the peak activity of the renin-angiotensin-aldosterone system and subsequently decrease nocturnal blood pressure levels.[15]

Dihydropyridine calcium channel blockers (CCB) consistently lower blood pressure both during the daytime and nighttime, irrespective of the timing of their administration. Multiple studies have demonstrated that the efficacy of amlodipine in reducing blood pressure is consistent regardless of the timing of delivery, indicating that it is not influenced by circadian rhythm. The administration of a sustained-release oral (SRO) formulation of isradipine in the evening resulted in the restoration of the typical 24-hour blood pressure and heart rate patterns in individuals with nocturnal hypertension caused by renal conditions. In contrast, the administration of nisoldipine extended-release in the morning resulted in lesser elevations in sleep and early morning heart rate, while still exhibiting similar hypotensive effects in individuals diagnosed with mild-to-moderate hypertension.[13,15]

The use of loop diuretics and hydrochlorothiazide before bedtime has been shown to have a more pronounced impact on blood pressure fluctuations. The regulation of blood pressure through β adrenoceptor generally exhibits a notable effect during diurnal periods, while its impact during nocturnal and early morning hours is rather insignificant. The administration of α-blockers during the evening has been observed to have a peak hypotensive impact during the early morning hours, a time when vascular tone is heightened. The determination of the optimal dose time may be individualized for each person, especially when many medications are being administered.[13–15]

7. Bedtime Or Morning Administration Of Antihypertensive Drugs In Clinical Trials

The Hygia Chronotherapy Trial was a major study undertaken within the primary care system to examine whether administering hypertension medication before bedtime, as opposed to upon rising, results in greater cardiovascular disease (CVD) risk reduction. The experiment included a total of 19,000 individuals diagnosed with hypertension, and the median duration of follow-up was 6.3 years. The results revealed that individuals who adhered to a bedtime regimen for their hypertension medication exhibited a notably reduced likelihood of encountering the primary cardiovascular disease (CVD) outcome, encompassing CVD-related mortality, myocardial infarction, coronary revascularization, heart failure, or stroke, in comparison to those who administered their medication upon awakening.[16]

The Treatment in Morning versus Evening (TIME) trial was done to evaluate the potential advantages of delivering blood pressure drugs in the evening as opposed to the morning, specifically focusing on hypertensive persons. The study encompassed a cohort of individuals with hypertension who were subjected to a random assignment, dividing them into two groups: one receiving blood pressure medications in the evening (between 8:00 pm and midnight), and the other group receiving meds in the morning (between 6:00 am and 10:00 am). The findings of the TIME study indicate that patients have the flexibility to choose between morning or evening administration of antihypertensive treatment based on their own preferences. In the population of individuals diagnosed with hypertension, there is no significant impact on the occurrence of adverse cardiovascular events based on the timing of administration of blood pressure drugs. No safety problems were observed with the administration of antihypertensive treatment in the evening.[17]

The MAPEC trial, a randomized controlled trial, sought to examine the impact of administering at least one antihypertensive medication at bedtime compared to upon waking, in order to assess its efficacy in reducing cardiovascular morbidity and mortality. The research encompassed a total of 2,156 individuals diagnosed with hypertension, and the duration of observation for each participant had a median value of 5.6 years. The study's authors reached the conclusion that the implementation of this uncomplicated intervention resulted in enhanced blood pressure management and a little decrease in cardiovascular incidents.[18]

The Harmony experiment, also known as the Hellenic-Anglo Research into Morning or Night Antihypertensive Drug Delivery trial, was a randomized crossover trial that aimed to assess potential variations in ambulatory blood pressure monitoring levels based on the timing of drug delivery. The study enrolled individuals between the ages of 18 and 80 who had hypertension that was reasonably controlled, with blood pressure levels not exceeding 150/90 mm Hg. These individuals were also required to be on a stable treatment regimen consisting of at least one antihypertensive medication. The recruitment process took place at two medical centers located in London and Thessaloniki. The trial's findings indicate that the timing of antihypertensive medicine delivery, whether in the morning or evening, did not have a significant impact on the average 24-hour or clinic blood pressure levels of hypertensive patients who already had relatively well-controlled blood pressure.[19]

The BedMed trial is a study that follows a prospective, randomized design. It is an open-label experiment with blinded end-points. The research intends to evaluate the potential impact of delivering antihypertensive medication at bedtime, as opposed to the traditional morning administration, on the occurrence of significant adverse cardiovascular events. The study encompasses a cohort of primary care patients with hypertension who are currently undergoing treatment with antihypertensive medication and do not exhibit any signs or symptoms of glaucoma. Invitations were delivered by primary care providers in five Canadian jurisdictions, namely British Columbia, Alberta, Saskatchewan, Manitoba, and Ontario, to patients who met the eligibility criteria. The individuals who provided consent were randomly assigned to receive all antihypertensive medications either in the evening or in the morning through a centralized randomization process. The principal endpoint encompasses a combination of mortality from any cause or hospitalization due to myocardial infarction/acute coronary syndrome, stroke, or congestive heart failure. The secondary outcomes encompass the individual components of the primary outcome, namely all-cause hospitalization or emergency department visit, admission to long-term care, occurrence of non-vertebral fracture, diagnosis of new glaucoma, decline in cognitive function at the 18-month mark compared to baseline (measured using the Short Blessed Test), and a few other selected outcomes. The ongoing BedMed trial is now in progress.[20]

8. Ingestion-Time Effects Of Hypertension Treatment On Safety

The administration of antihypertensive medications at bedtime is widely accepted and well tolerated in the majority of clinical investigations. Nevertheless, the nocturnal decrease in blood pressure may present potential hazards for numerous people in the event of an extreme decline in blood pressure during the nighttime. The phenomenon of over-dipping or extreme-dipping, characterized by a significant decrease in nocturnal blood pressure surpassing 20%, has been associated with a heightened susceptibility to myocardial ischemia in individuals diagnosed with coronary heart disease, as well as with the occurrence of silent cerebral infarcts. The hazards associated with these conditions are notably elevated in geriatric populations. Elderly people with nocturia may face an increased risk of falls due to nocturnal hypotension. Additionally, it should be noted that a decrease in blood pressure throughout the night is also considered a contributing factor to the advancement of visual field deterioration in those diagnosed with glaucoma.[13]

9. Conclusion

Circadian rhythms have a significant impact on various homeostatic parameters, including blood pressure, which fluctuates with the day and night cycle. Research studies have demonstrated that nocturnal blood pressure measurements possess more prognostic value in predicting cardiovascular and all-cause mortality outcomes among individuals with hypertension, compared to systolic blood pressure readings taken during daytime hours. All experts endorse 24-hour ambulatory BP monitoring as the best method for measuring BP and personalizing hypertension therapy.

Current research studies present some ambiguity regarding the benefits of administering hypertension drugs in the morning versus the evening. At present, a major study, known as the BedMed trial, is being conducted to evaluate the impact of administering hypertension drugs at bedtime compared to the conventional morning administration on cardiovascular outcomes (mortality from any cause or hospitalization due to myocardial infarction/acute coronary syndrome, stroke, or congestive heart failure). This study could potentially serve as a reference for improved hypertension management in the future.

10 . Declaration

10.1 Ethics Approval and Consent to participate
Not applicable.

10.2. Consent for publication
Not applicable.

10.3 Availibility of data and materials
Data used in our study were presented in the main text.

10.4 Competing interests
Not applicable.

10.5 Funding Source
Not applicable.

10.6 Authors contributions
Idea/concept: MF. Design: MF. Control/supervision: CTT. Data collection/processing: MF. Analysis/interpretation: MF, CTT. Literature review: MF. Writing the article: MF. Critical review: CTT. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

10.7 Acknowledgements
We thank to Brawijaya Cardiovascular Research Center

References

1. Costello HM, Gumz ML. Circadian Rhythm, Clock Genes, and Hypertension: Recent Advances in Hypertension. *Hypertension*. 2021;78(5):1185-1196. doi:10.1161/HYPERTENSIONAHA.121.14519

2. 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*. 2021;57:41-48. doi:10.1016/j.coph.2020.10.014

3. Hermida RC, Hermida-Ayala RG, Smolensky MH, Mojón A, Fernández JR. Ingestion-time differences in the pharmacodynamics of hypertension medications: Systematic review of human chronopharmacology trials. *Adv Drug Deliv Rev*. 2021;170:200-213. doi:10.1016/j.addr.2021.01.013

4. Rabinovich-Nikitin I, Lieberman B, Martino TA, Kirshenbaum LA. Circadian-Regulated Cell Death in Cardiovascular Diseases. *Circulation*. 2019;139(7):965-980. doi:10.1161/CIRCULATIONAHA.118.036550

5. Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Circadian rhythms and cardiovascular health. *Sleep Med Rev*. 2012;16(2):151-166. doi:10.1016/j.smrv.2011.04.003

6. Thoonkuzhy C, Rahman M. New Insights on Chronotherapy in Hypertension: Is Timing Everything? *Curr Hypertens Rep*. 2020;22(4). doi:10.1007/s11906-020-1032-x

7. Kario K, Hoshide S, Chia YC, et al. Guidance on ambulatory blood pressure monitoring: A statement from the HOPE Asia Network. *J Clin Hypertens*. 2021;23(3):411-421. doi:10.1111/jch.14128

8. Kario K, Hoshide S, Chia YC, et al. Guidance on ambulatory blood pressure monitoring: A statement from the HOPE Asia Network. *J Clin Hypertens*. 2021;23(3):411-421. doi:10.1111/jch.14128

9. Huang QF, Yang WY, Asayama K, et al. Ambulatory Blood Pressure Monitoring to Diagnose and Manage Hypertension. *Hypertension*. 2021;77(2):254-264. doi:10.1161/HYPERTENSIONAHA.120.14591

10. Ziegler MG, Milic M. Sympathetic nerves and hypertension in stress, sleep apnea, and caregiving. *Curr Opin Nephrol Hypertens*. 2017;26(1):26-30. doi:10.1097/MNH.0000000000000288

11. O'Brien E, Parati G, Stergiou G, et al. European society of hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens*. 2013;31(9):1731-1768. doi:10.1097/HJH.0b013e328363e964

12. Sogunuru GP, Kario K, Shin J, et al. Morning surge in blood pressure and blood pressure variability in Asia: Evidence and statement from the HOPE Asia Network. *J Clin Hypertens*. 2019;21(2):324-334. doi:10.1111/jch.13451

13. 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):1396-1406. doi:10.1097/HJH.0000000000002532

14. Kumar B, Chawla O, Bhattacharjee M, Singh A. Circadian rhythm of blood pressure: Implications for antihypertensive management. *Indian Journal of Medical Specialities*. 2021;12(2):53. doi:10.4103/injms.injms_4_21

15. De Giorgi A, Mallozzi Menegatti A, Fabbian F, Portaluppi F, Manfredini R. Circadian rhythms and medical diseases: Does it matter when drugs are taken? *Eur J Intern Med*. 2013;24(8):698-706. doi:10.1016/j.ejim.2013.03.019

16. Mathur P, Kadavath S, Marsh JD, Mehta JL. Chronotherapy for hypertension: Improvement in patient outcomes with bedtime administration of antihypertensive drugs. *Eur Heart J*. 2020;41(48):4577-4579. doi:10.1093/eurheartj/ehz836

17. Mackenzie IS, Rogers A, Poulter NR, et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. *The Lancet*. 2022;400(10361):1417-1425. doi:10.1016/S0140-6736(22)01786-X

18. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of circadian time of hypertension treatment on cardiovascular risk: Results of the MAPEC study. *Chronobiol Int*. 2010;27(8):1629-1651. doi:10.3109/07420528.2010.510230

19. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903-1913. doi:10.1016/S0140-6736(02)11911-8

20. Garrison SR, Kolber MR, Allan GM, et al. Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial. *BMJ Open*. 2022;12(2). doi:10.1136/bmjopen-2021-059711