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REVIEW ARTICLE

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Circadian rhythms in cardiovascular physiology and disease: extrinsic and intrinsic factors with implications for intensive care

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ABSTRACT

Introduction. Circadian rhythms are endogenous, approximately 24-hour oscillations that coordinate nearly all physiological systems, including cardiovascular function. The suprachiasmatic nucleus serves as the central pacemaker, synchronizing peripheral clocks in the heart, vasculature, and kidneys to generate daily fluctuations in blood pressure, heart rate, endothelial function, coagulation, myocardial metabolism, and autonomic tone. Disruption of circadian organization – through extrinsic factors (shift work, irregular light exposure, altered feeding schedules) or intrinsic factors (aging, inflammation, genetic clock-gene variants) – has been strongly linked to increased cardiovascular morbidity and mortality.

Material and methods. A bibliographic search was conducted in PubMed, Scopus, and Web of Science for English-language publications (2000–2025), focusing on the circadian rhythm, cardiovascular disease, hypertension, chronotherapy, and critical illness. Keywords included “circadian rhythm,” “cardiovascular disease,” “hypertension,” “chronotherapy,” and “intensive care.” Original research, clinical trials, meta-analyses, and experimental studies were eligible; studies addressing circadian blood pressure variability and its relation to outcomes in critically ill patients were specifically examined. Filters required full-text availability and publication dates from 2000 to 2025. The search yielded 276 full-text articles, of which 79 representative sources were selected for this narrative review.

Results. This review synthesizes current evidence demonstrating that circadian clocks regulate essential cardiovascular processes and that their disruption contributes to disease pathogenesis. Observational data on circadian blood pressure variability are discussed, showing that the attenuation of normal hemodynamic oscillations is associated with a worse prognosis. Particular attention is given to the extrinsic and intrinsic factors that modulate circadian alignment, with implications for the management of patients in intensive care.

Keywords: circadian rhythm, cardiovascular disease, hypertension, chronotherapy, autonomic dysfunction, intensive care.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Regarding the role of the circadian rhythm in cardiovascular physiology, the prognostic significance of circadian blood pressure variability in critically ill patients remains insufficiently explored. In particular, the relationship between circadian hemodynamic alterations and mortality risk in intensive care settings is not yet fully understood. Furthermore, the integration of circadian parameters with established clinical severity scores to improve prognostic assessment has not been extensively investigated.

The research hypothesis

We hypothesized that the disruption of physiological circadian blood pressure variability is associated with increased mortality in

critically ill patients. Furthermore, we assumed that the incorporation of circadian hemodynamic parameters into established clinical severity scoring systems, such as SOFA and APACHE II, could improve prognostic accuracy and provide additional information regarding patient outcomes.

The novelty added by the manuscript to the already published scientific literature

The present manuscript provides new insights into the prognostic significance of circadian blood pressure variability in critically ill patients. The integration of circadian variability into established prognostic scores may contribute to improved risk stratification and support the development of chronotherapeutic approaches in intensive care medicine.

Introduction

Because the Earth turns on its axis every 24 hours, almost all life on the planet has a mechanism – circadian rhythmicity – to anticipate the daily changes caused by this rotation. The molecular clocks that control circadian rhythms are being revealed as important regulators of physiology and disease. In humans, circadian rhythms have been studied extensively in the cardiovascular system. Many cardiovascular functions, such as endothelial function, thrombus formation, blood pressure, and heart rate, are now known to be regulated by the circadian clock. Additionally, the onset of acute myocardial infarction, stroke, arrhythmias and other adverse cardiovascular events shows circadian rhythmicity [1].

The circadian clock evolved in diverse organisms to integrate external environmental changes with internal physiology. The clock endows the host with temporal precision and robust adaptation to the surrounding environment. When circadian rhythms are perturbed or misaligned—as a result of jet lag, shift work, or other lifestyle factors—adverse health consequences arise, and the risks of diseases such as cancer, cardiovascular diseases, or metabolic disorders increase. Although the negative impact of circadian rhythm disruption is now well established, how to take advantage of biological timing, or correct it for health benefits, remains underappreciated [2].

The circadian clock is an evolutionarily conserved biological system that coordinates physiological and behavioral processes in a 24-hour rhythm, enabling organisms to anticipate and adapt to daily environmental changes, such as the light-dark cycle [3, 4]. At its core, the circadian rhythm is governed by a network of molecular clocks, with the suprachiasmatic nucleus (SCN) in the hypothalamus serving as the central pacemaker that synchronizes peripheral clocks located in virtually all tissues, including the heart, blood vessels, and kidneys [5-7]. The circadian rhythm, orchestrated by the SCN, synchronizes body-wide clocks through neural and hormonal pathways. Light signals, detected by specialized retinal cells, travel via the retinohypothalamic tract to the SCN, initiating a cascade through the paraventricular nucleus (PVN), brainstem, and spinal cord to the pineal gland. The molecular machinery of the circadian clock involves a set of core clock genes, including *CLOCK*, which operate via transcriptional-translational feedback loops (TTFLs) to regulate the expression of clock-controlled genes (CCGs) that influence diverse physiological processes [3, 8]. This intricate system ensures temporal coordination

of cardiovascular functions, such as blood pressure, heart rate, and endothelial function, which exhibit robust diurnal variations [9-12]. For instance, blood pressure typically dips during sleep and rises in the early morning, a pattern regulated by the interplay between the SCN and peripheral clocks in the cardiovascular system (CVS) [13-16]. Disruption of these rhythms, as seen in shift workers or individuals with sleep disorders, has been epidemiologically linked to an increased risk of cardiovascular disease (CVD), including hypertension, myocardial infarction (MI), and atherosclerosis [17, 18]. Studies have shown that circadian misalignment can lead to dysregulation of the autonomic nervous system (ANS), impaired glucose metabolism, and increased systemic inflammation, all of which contribute to CVD pathogenesis [19-22]. Evidently, the circadian rhythm is a crucial conduit between the brain and the heart.

The objective of this narrative review is to synthesize the current scientific evidence on the regulation of cardiovascular physiology by circadian rhythms and the consequences of their disruption in disease states. Specifically, we aim to: (1) delineate the molecular and physiological mechanisms linking central and peripheral circadian clocks to key cardiovascular functions (blood pressure, heart rate, endothelial function, coagulation, and autonomic tone); (2) analyze the contributions of extrinsic (e.g., shift work, irregular light exposure, altered feeding schedules) and intrinsic (e.g., aging, inflammation, genetic clock-gene variants) factors to circadian misalignment and its associated cardiovascular morbidity and mortality; and (3) discuss the clinical implications of these disruptions for critically ill patients in intensive care, including the potential value of chronotherapeutic strategies and circadian-aligned environmental interventions.

Material and methods

A comprehensive bibliographic search was initiated to conduct a narrative literature review synthesizing current scientific evidence regarding circadian rhythm disruption and its effects on cardiovascular regulation in critically ill patients. The review followed the general principles of systematic literature analysis to identify, select, and evaluate relevant studies addressing circadian mechanisms and their clinical implications in intensive care settings. The search was performed across electronic databases, including PubMed, Scopus, and Web of Science, and was limited to studies published between 2000 and 2025. The following keywords and their combinations were used: *circadian rhythm*, *circadian disruption*, *blood pressure variability*,

cardiovascular regulation, critical illness, intensive care unit, chronobiology, and hemodynamic instability. Additionally, the reference lists of relevant publications were manually screened to identify further studies that met the inclusion criteria. Studies were considered eligible if they addressed circadian rhythm physiology, mechanisms of circadian regulation, circadian disruption in intensive care environments, or the relationship between circadian rhythms and cardiovascular function.

The following types of publications were included:

- clinical studies
- experimental studies
- observational studies
- relevant review articles

Studies were excluded if they:

- were not published in English
- lacked relevance to the topic of circadian rhythm and cardiovascular regulation
- did not include data or discussion related to critically ill patients or cardiovascular physiology.

The identified articles were initially screened based on their titles and abstracts. Publications that appeared relevant were further assessed through full-text evaluation. Studies meeting the eligibility criteria were included in the final analysis. Relevant information from the selected studies was extracted, including:

- study objectives
- study design
- investigated circadian parameters
- cardiovascular outcomes
- major findings related to circadian rhythm disturbances.

The extracted data were organized and analyzed to identify key themes related to circadian regulation and cardiovascular instability in critically ill patients. The findings from the selected studies were qualitatively synthesized to provide an integrated overview of the current understanding of circadian rhythm disruption and its clinical implications in intensive care medicine. As this study represents a review of previously published literature, no original statistical analyses were performed; instead, the results from the included studies were analyzed descriptively. Because this study is based exclusively on previously published scientific literature, ethical approval and informed consent were not required.

The literature search identified 276 records through database searching across PubMed, Scopus, and Web of Science. After screening titles and abstracts, 197 studies were excluded due to a lack of relevance, insufficient data, or non-English language. A total of 82 full-text articles were assessed for eligibility and included in the final review (Fig. 1).

Results

It is undeniable that the circadian orchestration of biological processes is fundamental for both health and disease. During pathological conditions, circadian orchestration is often perturbed, and the disruption of normal

rhythms in healthy organisms leads to pathology. Acknowledgment of these principles has led to the concept that perhaps circadian clocks and biology might be targeted for cardiovascular disease treatment [23]. Disruption of normal circadian rhythms, whether through behavioral, environmental, or genetic means, is detrimental in both humans and animal models, leading to an increased risk of pathologies, including cardiovascular disease. Similarly, whole-body circadian rhythmicity is attenuated with age, in association with increased disease risk [24]. Taken together, such observations suggest that the maintenance of normal circadian biology is critical for prevention of disease and maximizing longevity [23]. The master biological clock, known as the central clock, is located in the suprachiasmatic nucleus (SCN) in the hypothalamus [25]. The central clock is essentially involved in adjusting circadian variations in physiological function by regulating the autonomic nervous system, humoral mediators, and other systemic signals. In addition to the central clock in the SCN, each peripheral organ and cell also possesses circadian expression of core clock genes; these are referred to as peripheral clocks. The molecular mechanisms of peripheral clocks are believed to be identical to those of the central clock [26]. The factors that can reset and affect the phase of the internal clock are called zeitgebers (timekeepers). Light is established as the main zeitgeber for the central clock. In contrast, the specific zeitgebers for peripheral clocks are not yet fully elucidated. The discovery of the appropriate zeitgeber for each organ is required to establish novel therapeutic approaches considering time-of-day treatment, namely chronotherapy [27].

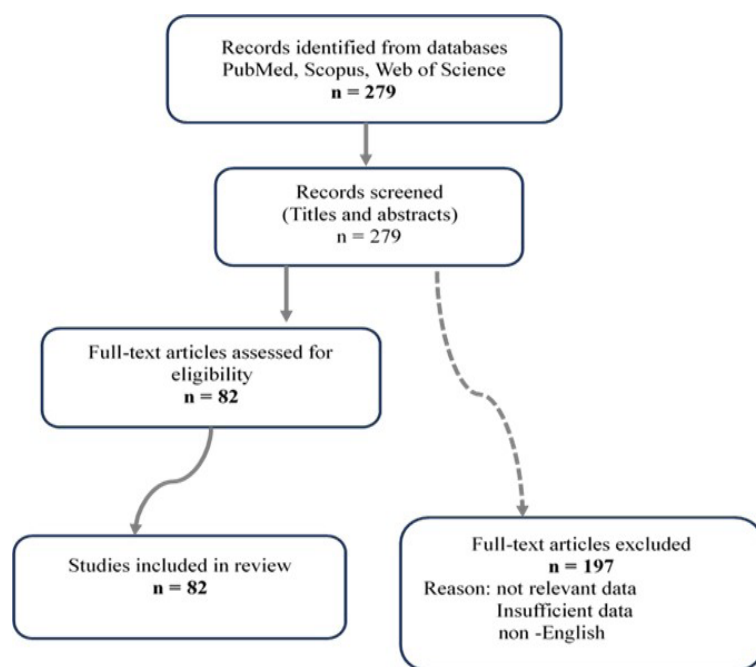


Fig. 1 PRISMA 2020 flow diagram of the literature search and study selection process

The circadian mechanism underlies daily rhythms in cardiovascular physiology, and rhythm disruption is a major risk factor for heart disease and worse outcomes. However, the role of circadian rhythms is generally clinically unappreciated [28]. These rhythms drive daily variations in key parameters, including heart rate [29], blood pressure [30], and cardiac contractility [31]. Circadian rhythm disruption is a major risk factor for cardiovascular disease and is associated with severe health consequences. [32, 33]. Recently, there have been major advances in our understanding of daily rhythmicity and its relevance to the pathogenesis and treatment of cardiac hypertrophy and heart failure [31, 34, 35].

Because circadian rhythms display oscillating patterns, developing treatments that can take advantage of this biological governance holds great therapeutic value. Hence, a crucial therapeutic approach involves mitigating risks during periods of highest vulnerability in the circadian cycle, or reinstating typical circadian phase and amplitude patterns [36].

Circadian rhythms, regulated by the suprachiasmatic nucleus in the brain, profoundly influence cardiovascular health through intricate neurobiological mechanisms. These rhythms regulate gene expression in cardiomyocytes, modulate autonomic nervous system (ANS) activity, and synchronize cardiovascular functions with environmental cues, ultimately impacting heart rate, blood pressure, and susceptibility to cardiac events. The intricate relationship between circadian rhythms and cardiovascular health emphasizes the critical role of brain-heart communication in physiological processes [37].

Peripheral clocks in cardiovascular tissues. Peripheral clocks in cardiovascular tissues play a crucial role in regulating circadian rhythms of cardiovascular function, working in concert with the central clock in the SCN [3, 38, 39]. In the heart, cardiomyocytes exhibit rhythmic expression of core clock genes and CCGs, with up to 10 % of the cardiac transcriptome showing circadian oscillations [40]. These oscillations regulate critical cardiac functions, such as the expression of ion channels like $K_v1.5$, $K_v4.2$, and $Scn5a$, which are involved in cardiac electrophysiology [41, 42]. The peripheral clock in blood vessels also demonstrates circadian rhythmicity, with smooth muscle BMAL1 participating in blood pressure regulation [13, 43]. Beesley et al. conducted an intriguing study to explore how circadian rhythms affect heart function in mice cardiomyocytes. They found that the circadian clock gene expression of PER2 in cardiomyocytes is cell-autonomous and can be amplified by β -adrenergic signaling, suggesting how circadian rhythms are regulated in cardiomyocytes and their potential implications for cardiac function [44]. Endothelial cells, crucial for vascular homeostasis, exhibit circadian control over coagulation factors like plasminogen activator inhibitor-1 (PAI-1) and thrombomodulin, as well as cell cycle regulators *Ccna1* and *Cdk1* [40, 45, 46]. The interaction between central and peripheral clocks is complex, with the SCN playing a central role in the synchronization of peripheral clocks

through neural and humoral signals [47, 48]. However, peripheral clocks can also be affected by local zeitgebers, such as food intake and physical activity, allowing for tissue-specific temporal organization [46, 49, 50]. This intricate network of central and peripheral clocks enables the CVS to anticipate and adapt to daily environmental changes. The SCN affects peripheral clocks via the SNS, while hormones like T_3 and neurotransmitters such as VIP fine-tune cardiac rhythms. Voltage-gated calcium channels (VGCCs) play a crucial role in translating circadian signals into functional cardiac outputs [40, 51]. Disruption of this synchronization, either between the central clock and peripheral clocks or among different peripheral clocks, can lead to cardiovascular dysfunction [52]. For instance, cardiomyocyte-specific deletion of the *Bmal1* gene results in a slower heart rate and increased susceptibility to arrhythmias [41, 53, 54]. Moreover, desynchronization between internal clocks and the external environment, as seen in shift work or irregular social schedules, has been associated with an increased risk of cardiovascular diseases [20, 46]. Understanding the molecular mechanisms underlying these peripheral clocks and their interaction with the central clock is crucial for developing novel therapeutic approaches to manage cardiovascular disorders and optimize treatment timing, a concept known as chronotherapy [41, 46, 55, 56].

Mechanism of circadian disruption causing cardiovascular diseases. Studies have shown that major cardiovascular events, such as acute myocardial infarction, sudden cardiac death, and stroke, occur more frequently at certain times of the day – particularly in the early morning – suggesting a dysfunctional circadian regulation. Disruption of circadian rhythms has been associated with resistant hypertension, endothelial dysfunction, and chronic vascular inflammation, all of which contribute to the progression of cardiovascular disease.

Circadian disruption broadly refers to multiple types of circadian clock disturbances, including circadian misalignment [57] and circadian desynchrony [58] or desynchronization [59]. These disturbances can manifest across various biological levels, from cellular and tissue scales to organismal and systemic scales. Circadian misalignment is a mismatch between an individual's internal circadian clock and their external environment or social schedule. Circadian desynchrony or desynchronization both refer to a variance in the cycles of 2 or more rhythms. Both concepts can be quantified by measuring the phase angle differences and comparing the estimated durations of the rhythms [60].

Circadian disruption significantly impacts cardiovascular health through multiple interconnected mechanisms (Table 1). Dysregulation of ANS activity is a key factor, as evidenced by altered heart rate variability and blood pressure patterns in individuals experiencing circadian misalignment [20, 41, 46]. This disruption can lead to prolonged QTc intervals (the time from the start of the Q wave to the end of the T wave on an electrocardiogram (ECG), measuring ventricular depolarization and repolarization) and increased susceptibility to arrhythmias, particularly in shift workers

[38, 46]. Impaired metabolic and hormonal rhythms also play a crucial role in associating circadian disruption with CVD. Cortisol and melatonin, two hormones with strong circadian patterns, are particularly affected. Disrupted cortisol

rhythms can lead to increased inflammation and metabolic dysfunction, while altered melatonin secretion due to light exposure at night can impact sleep quality and cardiovascular function [50, 61, 62].

Table 1. Effects of circadian clock gene dysregulation on cardiovascular function

Clock gene manipulation	Cardiovascular effects	References
Bmal1 knockout	Arrhythmic behaviour, loss of circadian rhythms in peripheral tissues, reduced lifespan	Haque et al., 2019
Per2 mutation	Impaired endothelium-dependent relaxation, decreased nitric oxide production	Viswambharan et al., 2007
SCN-specific Bmal1 knockout	Loss of circadian behavioural rhythms while peripheral clocks remain rhythmic	Haque et al., 2019
Astrocyte-specific Bmal1 knockout	Delayed activity onset and slower entrainment to new light-dark cycles	Haque et al., 2019
Ventral forebrain Bmal1 knockout	Altered timing of circadian behavioural patterns	Haque et al., 2019
Per2 knockout in cardiomyocytes	Increased cell death and mitochondrial dysfunction under stress	Bhaskara et al., 2024
VSMC Bmal1 knockout	Aggravated atherosclerotic lesions, increased VSMC migration, ROS levels, and apoptosis	Lin et al., 2022
Postnatal cardiomyocyte Bmal1 knockout	Increased cardiac hypertrophy and fibrosis; pressure overload-induced cardiac remodeling	Liang et al., 2022
Per1 knockout	Circadian rhythm desynchronization and increased salt-sensitive hypertension	Zietara et al., 2022

Note: VSMC – vascular smooth muscle cells; ROS – reactive oxygen species; SCN – suprachiasmatic nucleus; BMAL1 – Brain and Muscle ARNT-Like 1, a core component of the circadian clock transcription-translation feedback loop; PER1 / PER2 – Period genes (Period Circadian Regulator 1 and 2), essential components of the negative feedback loop regulating circadian rhythms.

Oxidative stress and inflammation are exacerbated by circadian disruption, contributing significantly to CVD risk. Studies have shown that circadian rhythm disruption impairs tissue homeostasis and exacerbates chronic inflammation [39, 50, 63, 64]. Circadian dysregulation is intricately correlated to various cardio-vascular conditions, highlighting the critical role of the body’s internal clock in maintaining cardiovascular health. The onset of cardiovascular disease (CVD) exhibits a diurnal oscillation; for example, acute coronary syndrome or atrial fibrillation often occurs in the early morning (Table 2).

In addition to disease onset, several cardiac functions also show circadian variation, including heart rate (HR) and blood pressure (BP). Recent evidence supports the idea that the diurnal variation of cardiovascular physiology and pathology is tightly related to an intrinsic biological rhythm, named the circadian clock [27].

Table 2. Common onset time of cardiovascular events.

Disease	Onset time
Acute myocardial infarction	Early morning
Cerebral infarction	Morning
Subarachnoid hemorrhage	Daytime
Atrial fibrillation	Morning/night
Ventricular tachycardia/fibrillation	Morning

Diurnal variation and chronotherapy in blood pressure/hypertension. It is well known that there is a 24-hour variation in BP with a distinct peak in the morning. This daily variation in BP is considered representative of both

intrinsic and exogenous factors. Intrinsic factors include autonomic nervous system activity and humoral factors such as cortisol, renin, aldosterone, vasoactive intestinal peptide, and ANP [65]. Conversely, exogeneous factors such as physical activity, emotional state, meals, and sleep-wake states also profoundly affect BP variations. In normal subjects, the nocturnal BP decline of less than 10-20%, and these individuals are termed “normal dippers”. Persons with a nocturnal decline of less than 10% are classified as “non-dippers”. Some subjects can be classified as “extreme dippers” (a decline greater than 20%), while others present as “inverse dippers” or “risers” (a decline less than 0%), indicating that their asleep BP is higher than their awake BP (Table 3) [27].

Table 3. Indices of diurnal blood pressure (BP) decline.

BP Dipping Classification	Nocturnal BP decline ratio
Normal dipper	10–20%
Non-dipper	<10%
Extreme dipper	>20%
Inverse dipper/ riser	<0%

Note: $[(\text{Mean SBP awake} - \text{Mean SBP asleep}) / \text{Mean SBP awake}] \times 100$.

Loss of adequate BP decline during the sleep period may be a significant risk factor for cardiovascular organ damage. Hypertensive patients with the non-dipper BP pattern are found to be more susceptible to heart and kidney damage [66]. Patients with a non-dipper BP profile have a higher risk than dipper patients for left ventricular hypertrophy, heart failure, myocardial infarction, stroke, albuminuria, and progression to end-stage renal disease [65]. Non-dip-

per normotensive patients exhibit an equivalent hazard ratio for cardiovascular mortality compared to dipper hypertensive patients [66]. Inverse-dipper or riser patients also demonstrate a significantly higher incidence of stroke compared with those with other patterns of BP variation, suggesting that patients with this BP profile carry the highest overall risk for cardiovascular events [67, 68]. Considering the heterogeneity of BP profiles, it is clinically inappropriate to treat all hypertensive patients with the same regimen. Currently, more than 80% of hypertensive patients take all of their anti-hypertensive medications in the morning. Therefore, it is becoming a physician's responsibility to personalize treatment according to a patient's specific diurnal BP profile. Chronotherapy aims to provide treatment with maximum beneficial effects and minimal adverse effects by aligning drug delivery with the intrinsic circadian rhythm of disease processes or symptoms. Chronotherapy with antihypertensive medication can be successfully achieved by adjusting the administration time within a 24-hour cycle [27, 69].

Circadian rhythm in acute coronary syndrome. The onset of acute myocardial infarction (AMI) or pulmonary embolism demonstrates a clear circadian variation with a peak in the early morning [70, 71]. A number of cardiac functions related to the pathogenesis of myocardial infarction are known to exhibit circadian variation. Even the shift to daylight saving time in the spring could influence the onset of AMI; during the first 3 weeks after this seasonal transition, the incidence of AMI significantly increases [72].

The diurnal variation in autonomic nervous system activity could account for the circadian onset of AMI. In the early morning, systolic BP and HR increase, resulting in an elevated myocardial oxygen demand. Conversely, the vascular tone of the coronary arteries rises, and coronary blood flow decreases during morning hours. This mismatch between myocardial oxygen demand and supply in the morning appears to trigger the circadian onset of AMI. Interestingly, of the morning peak in AMI onset is blunted in patients receiving β -blockers, as well as in diabetic patients with autonomic neuropathy, highlighting the central role of autonomic nervous system signaling in driving this diurnal variation [73]. In addition, a state of hypercoagulability in the morning may underlie the circadian onset of AMI. Circulating platelet counts and platelet aggregation pathways fluctuate in a circadian fashion [74]. Because platelets are activated by catecholamines, the rhythmic activation of the autonomic nervous system can induce corresponding oscillations in platelet activity. The coagulation activity also has a circadian variation. The plasma concentration of factor VII, the elevation of which is known as a risk factor for coronary artery disease, exhibits a diurnal oscillation [75]. Other coagulation-related factors, such as fibrinogen, prothrombin, factor VIII, and tissue factor pathway inhibitor also exert circadian activation [76]. The coagulation process can be counterbalanced by activation of the fibrinolytic pathway, which attenuates the coagulation processes and prevents thrombosis. The fibrinolytic function, however, decreases

in the morning. Tissue plasminogen activator inhibitor-1 (PAI-1) regulates the activity of tissue plasminogen activator (t-PA), thus strongly influencing fibrinolytic activity. The concentration and activity of PAI-1 were noted to oscillate in a circadian pattern with a peak in the morning, resulting in lower t-PA activity during the morning. Therefore, the efficacy of t-PA therapy to restore the patency of occluded vessels in AMI patients is time-dependent [77]. As such, the circadian variation of PAI-1 activity seems to be strongly related to the morning decrease in fibrinolytic activity [27].

Sudden cardiac arrest is a malfunction of the heart's electrical system, typically caused by ventricular arrhythmias, that can lead to sudden cardiac death (SCD) within minutes. Epidemiological studies have shown that SCD and ventricular arrhythmias are more likely to occur in the morning than in the evening, and laboratory studies indicate that these daily rhythms in adverse cardiovascular events are at least partially under the control of the endogenous circadian timekeeping system. However, the biophysical mechanisms linking molecular circadian clocks to cardiac arrhythmogenesis are not fully understood [78].

The biophysical mechanisms underlying these daily rhythms in adverse cardiovascular events are not fully understood. The master circadian (24-hour) pacemaker in the hypothalamus, the suprachiasmatic nucleus (SCN), influences a variety of cardiovascular phenomena by coordinating daily rhythms in the release of hormones and other circulating molecules. Recently, it has been demonstrated that circadian clocks within heart muscle cells (cardiomyocytes) also regulate rhythms in cardiac electrophysiology [79].

Normal circadian organization is critical for maintaining homeostasis, and a disturbance of this rhythm can induce the progression of organ damage. Therefore, the dysregulation of the circadian rhythm can induce the development of cardiac diseases. Moreover, reversal of the deregulated circadian rhythm or resynchronization of individual tissue clocks may become a promising therapeutic target to prevent disease progression [27].

Discussion

The present review highlights the role of circadian regulation in cardiovascular physiology and its clinical implications in critically ill patients. Our findings support the concept that circadian blood pressure variability represents not only a physiological phenomenon but also a potential marker of systemic integrity and adaptive capacity. At the molecular level, circadian clock genes regulate myocardial metabolism, electrophysiological stability, endothelial function, and vascular tone. Disruption of these mechanisms contributes to autonomic imbalance, oxidative stress, inflammatory activation, and prothrombotic states. These pathophysiological pathways provide a biological explanation for the well-documented morning predominance of acute myocardial infarction, stroke, and malignant arrhythmias. Chronotherapeutic strategies, including time-adjusted antihypertensive administration and structured environmental light management, have demonstrated benefits

in non-ICU populations. However, evidence in critically ill patients remains limited. Prospective, multicenter studies are required to determine whether modulation of circadian patterns can improve survival and reduce cardiovascular complications in this vulnerable group [67, 72].

Several limitations should be acknowledged. The design of the reviewed studies restricts causal inference, and circadian assessment was limited to hemodynamic parameters without biochemical phase markers such as melatonin or cortisol. Additionally, standardized protocols for circadian monitoring in ICU practice are not yet established. Despite these limitations, the results support the hypothesis that preserved circadian variability reflects better physiological regulation and an improved prognosis.

The extrinsic and intrinsic factors discussed above acquire particular relevance in the intensive care environment, where multiple timers are simultaneously disrupted [79].

The study selection process, illustrated in the PRISMA 2020 flow diagram (Figure 1), enhances transparency and methodological rigor in the identification and inclusion of relevant studies. Several limitations should be acknowledged. The design of the reviewed studies restricts causal inference, and circadian assessment was limited to hemodynamic parameters without the inclusion of biochemical phase markers such as melatonin or cortisol. Additionally, standardized protocols for circadian monitoring in ICU practice are not yet established. Furthermore, although a comprehensive literature search was performed using major databases, along with language and full-text availability filters, no formal risk-of-bias assessment was conducted. Therefore, potential selection and publication biases cannot be fully excluded. The heterogeneity of the included studies in terms of design, patient populations, and outcome measures may also limit the generalizability of the findings.

Conclusions

The circadian system plays a vital role in regulating various physiologic processes. The way the body responds to injury is often dependent on the interaction of the injury with the circadian machinery. Circadian rhythms are frequently disrupted in patients in the ICU, and there are a number of factors that likely contribute to this breakdown. Practices leading to circadian rhythm optimization may improve patient outcomes, and the implementation of these practices should be incorporated into ICU care. Circadian rhythm disruption plays a significant role in cardiovascular pathology and is particularly relevant in critically ill patients. Incorporating circadian assessment into clinical evaluation may enhance prognostic accuracy and open new perspectives for individualized therapeutic timing in intensive care medicine.

Competing interests

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