

Review

Circadian Rhythms, Metabolic Disorders, and Cardiovascular Aging: Molecular Crosstalk and Clinical Translation

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ABSTRACT: Circadian rhythms play a crucial role in regulating physiological processes, and disruptions caused by aging, shift work, or irregular schedules are closely associated with metabolic dysfunction and accelerated cardiovascular aging. Age-related declines in circadian clock function contribute to metabolic imbalances and cardiovascular decline through pathways involving inflammation, oxidative stress, and mitochondrial dysfunction. Research has identified complex molecular networks linking circadian dysregulation to metabolic disorders and cardiovascular diseases, highlighting potential therapeutic targets such as sirtuin 1, peroxisome proliferator-activated receptor α , and reverse erythroblastosis virus α . Interventions based on circadian principles—such as time-restricted eating, chronotherapy, lifestyle modifications, and light therapy—exhibit promise in mitigating cardiovascular aging. However, several of these strategies require further validation in older adults, and challenges persist in clinical implementation owing to a lack of large-scale trials, population diversity, and real-world barriers. This review synthesizes current mechanistic evidence and underscores the necessity for personalized circadian-based approaches to enhance cardiovascular health in aging populations.

Keywords: Circadian rhythms, metabolic disorders, cardiovascular disease, aging

INTRODUCTION

Circadian rhythms are evolutionarily conserved across mammals, regulating essential physiological functions such as sleep–wake cycles, hormone secretion, and metabolic homeostasis [1]. Since the 1970s, research has established that cardiovascular functions, including blood pressure and heart rate, exhibit intrinsic circadian patterns, with the “morning surge phenomenon (early-morning blood pressure elevation)” identified as a key risk factor for acute cardiovascular events [2]. Further studies have demonstrated that circadian rhythms also closely regulate processes vital to cardiovascular health, including glucose metabolism, lipid homeostasis, and insulin secretion [3,4]. Emerging evidence suggests that circadian disruptions—such as those caused by shift work or irregular sleep—contribute to metabolic disorders such as diabetes and

obesity, which in turn increase the risk of hypertension, atherosclerosis, and other cardiovascular diseases [5,6]. Molecular studies in the early 21st century identified core clock genes (for example, *Clock*, *Bmal1*, *Per*, and *Cry*), whose mutations or dysregulation significantly affect metabolic and cardiovascular functions [7–9]. Peripheral tissues, including hepatic, adipose, myocardial, and vascular smooth muscle tissues, contain autonomous circadian clocks that synchronize with the central clock in the suprachiasmatic nucleus (SCN) to maintain metabolic–cardiovascular homeostasis [10,11]. Disruption of this central–peripheral synchronization accelerates vascular aging and cardiovascular disease progression through chronic inflammation, oxidative stress, and endothelial dysfunction (Fig. 1A) [12–14].

Importantly, metabolic dysfunction and circadian disruption interact synergistically, exacerbating

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cardiovascular aging [15]. As individuals age, the expression of core clock genes declines, eliciting metabolic imbalances and functional deterioration of the cardiovascular system [16]. For the purposes of this review, cardiovascular aging is defined as a progressive, multifactorial process characterized by (1) arterial stiffening and endothelial senescence; (2) cardiomyocyte hypertrophy, fibrosis, and mitochondrial decline; (3) electrophysiological remodeling and elevated arrhythmia risk; (4) impaired adaptive homeostasis and increased susceptibility to stress. This process is driven by intrinsic aging and aggravated by extrinsic factors, including circadian disruption, metabolic disease, and inflammation.

Systems biology approaches have revealed complex networks connecting circadian disruption, metabolic dysfunction, and cardiovascular aging [17–19]. Nevertheless, critical gaps persist, particularly concerning the functional diversity of clock genes across various cardiac cell types and the clinical applicability of circadian-based interventions. This review consolidates the most recent findings regarding the molecular mechanisms linking circadian rhythms, metabolic disorders, and cardiovascular aging; addresses ongoing controversies; outlines evidence-based clinical interventions. By incorporating circadian biology into cardiovascular care, we aim to establish a framework for personalized strategies to alleviate aging-related cardiovascular risk.

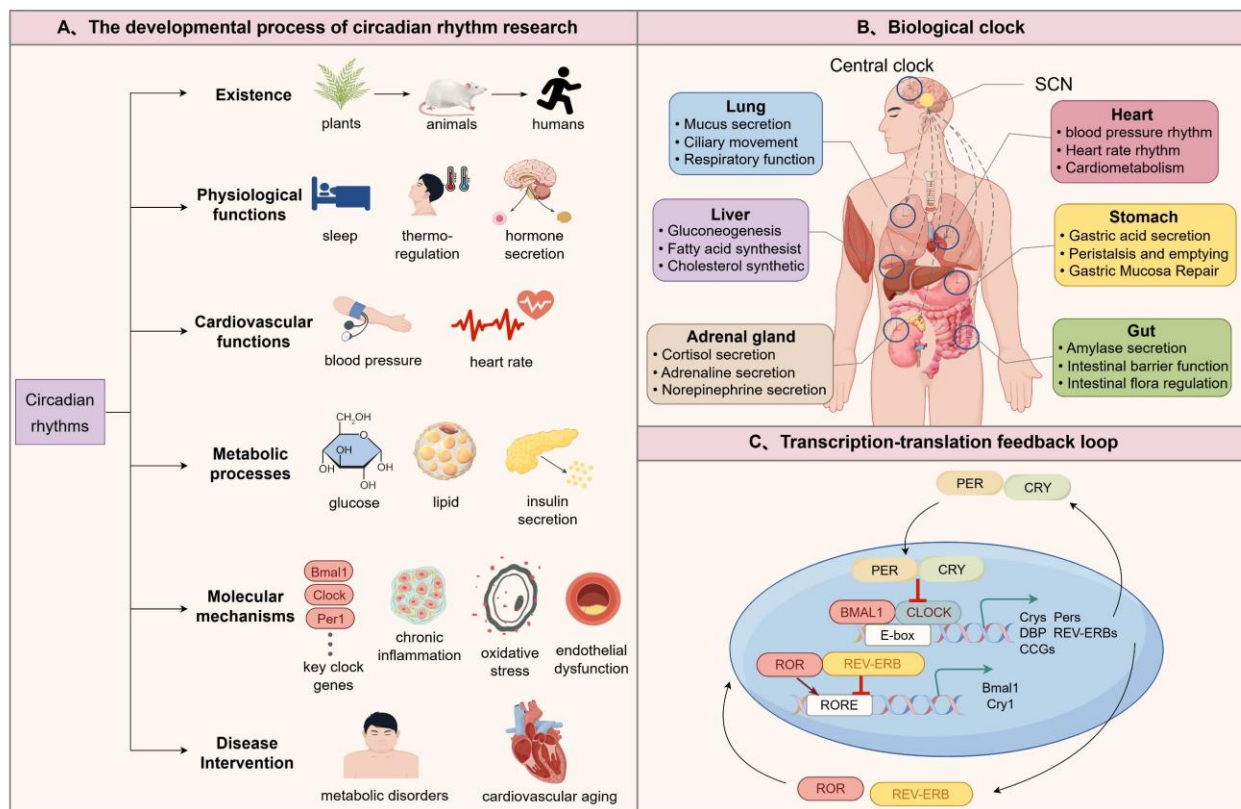


Figure 1. The development process and basic overview of the field of circadian rhythm research. (A) Timeline of major findings in circadian rhythms research ranging from the mid-20th century to now days; (B) Central and peripheral clocks: the central clock is located in the suprachiasmatic nucleus, then synchronises the peripheral clocks, found in all cells, via multiple direct and indirect routes. The peripheral clocks, control the circadian rhythm of several systems, including the endocrine, gastrointestinal, cardiovascular and respiratory system; (C) Core components of the molecular clock: a transcription-translation feedback loop involving transcription factors BMAL1 and CLOCK that bind to E-box response elements within promoter regions of target genes, including *Crys*, *Pers*, *DBP*, *REV-ERBs* and *CCGs* (positive arm). After being translated, *PER* and *CRY* dimerize and translocate back into the nucleus inhibiting *BMAL1/CLOCK* to repress their own transcription (negative arm). *ROR* activates *Bmal1* and *Cry1* transcription via interaction with *ROR* response elements, whereas *REV-ERB* inhibits *Bmal1* and *Cry1* (secondary loop). SCN suprachiasmatic nucleus; *CLOCK* circadian locomotor output cycles kaput; *BMAL1* brain and muscle arnt-like protein 1; *REV-ERB* reverse erythroblastosis virus α and β ; *PER* period protein; *CRY* cryptochrome; *ROR* retinoic acid-related orphan receptor; *RORE* *ROR* response elements; *CCGs* clock-controlled genes; *DBP* D site albumin promoter binding protein.

METHODS

Literature Search Strategy

To ensure a comprehensive and up-to-date review, we searched PubMed, Web of Science, and Embase from January 2000 to March 2026. The search utilized keywords related to circadian rhythm (for example, “circadian clock” and “clock gene”), metabolic disorder (for example, “type 2 diabetes,” “obesity,” and “insulin resistance”), and cardiovascular aging (for example, “vascular aging” and “cardiac aging”). Detailed search terms for each database are provided in Supplementary Material 1. Two authors (J.W. and Q.X.) independently screened titles, abstracts, and full texts, resolving

discrepancies through discussion with a third author (T.C.). We prioritized peer-reviewed original research, high-quality systematic reviews and meta-analyses, and human clinical studies, including foundational preclinical studies for mechanistic context. The exclusion criteria were as follows: non-English articles, letters, case reports, and studies unrelated to circadian–metabolic–cardiovascular aging. The focus is on studies published between 2021 and 2026. A summary table of key human studies for each intervention domain is included in the supplementary materials (Supplementary Table 1). Ultimately, 89 eligible studies were incorporated. Figure 2 presents a search and screening flowchart, compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

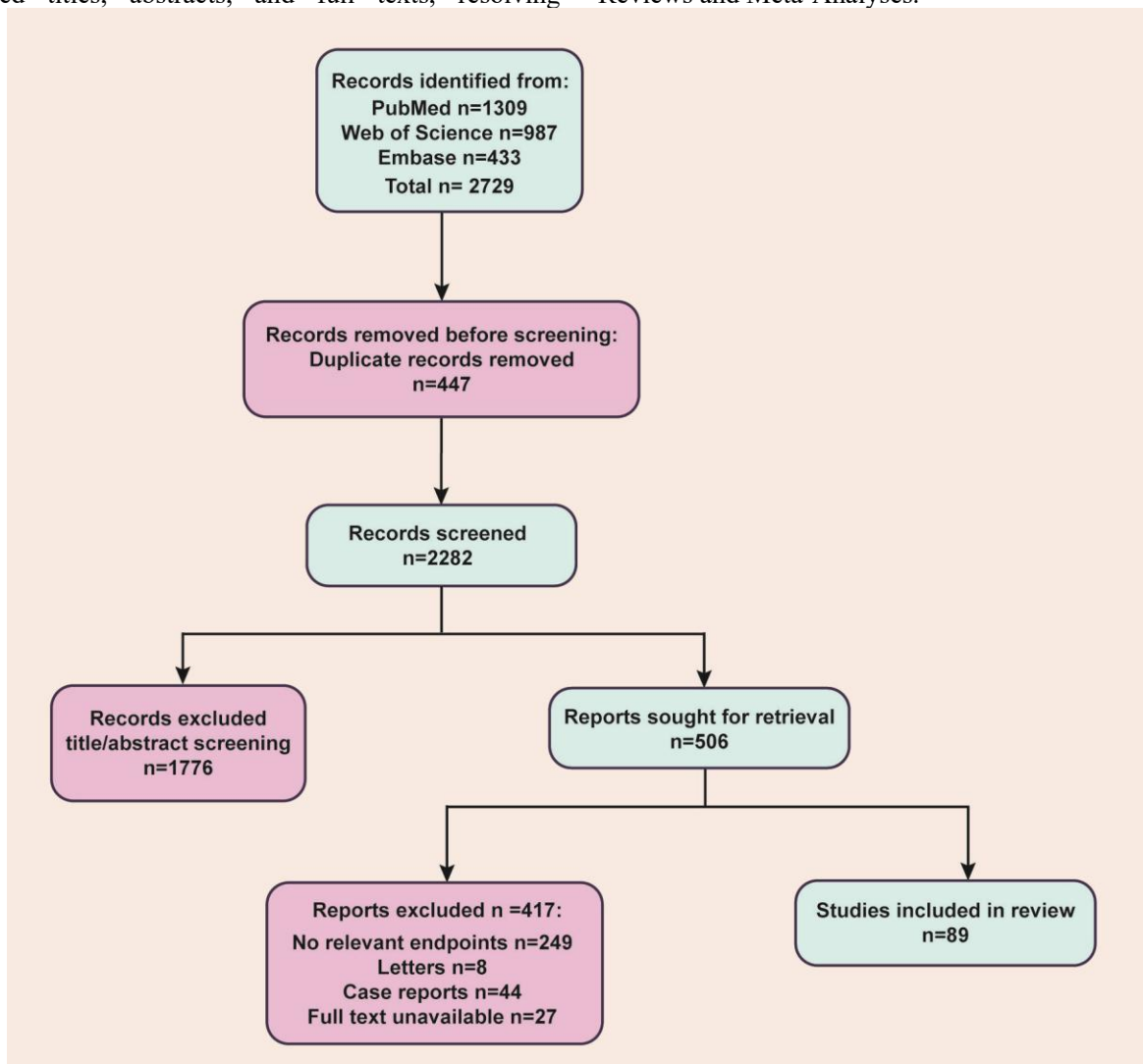


Figure 2. PRISMA flow diagram illustrates the literature search and study selection process. Records were retrieved from PubMed (n=1309), Web of Science (n=987), and Embase (n=433), totaling 2729 records. After removing 447 duplicates, 2282 unique records were screened by title and abstract, resulting in the exclusion of 1776 irrelevant records. Full-text articles of the remaining 506 records were assessed for eligibility. 417 records were excluded due to no relevant endpoints (n=249), letters (n=8), case reports (n=44), or unavailable full texts (n=27). Ultimately, 89 studies were included in the systematic review.

Evidence Grading

Evidence was classified into grades A, B, and C according to the 2024 revision of the European Society of Cardiology (ESC) evidence grading system, an internationally recognized framework developed by the ESC Clinical Practice Guidelines Committee.

Supplementary Table 2 summarizes the grading criteria. Key studies on circadian–metabolic–cardiovascular aging pathways and interventions were categorized into three groups—animal/preclinical, mechanistic human, and clinical outcome—and rated for robustness of evidence (Table 1).

Table 1. Evidence hierarchy for circadian-metabolic-cardiovascular aging pathways and interventions.

Category	Pathway/Intervention	Evidence Level (ESC 2024)	Justification	Reference
Animal/Preclinical	CLOCK/BMAL1 core clock regulation of metabolism and cardiovascular function	C	Preclinical mechanistic evidence only	[8, 35, 62, 65, 69, 74,75,86,92]
Animal/Preclinical	REV-ERB nuclear receptor signaling in metabolism and inflammation	C	Animal/cell models; awaiting human validation	[29,30,31,45,46,87,88,120,131]
Animal/Preclinical	PER/CRY proteins in vascular function and atherosclerosis	C	Animal/cell models; awaiting human validation	[52,53,67]
Animal/Preclinical	SIRT1/NAD ⁺ axis in circadian regulation of vascular aging	C	Animal studies; no human interventional data	[19,25,26,27]
Animal/Preclinical	PPAR α in metabolism and cardiovascular aging	C	Preclinical evidence	[28]
Animal/Preclinical	Mitochondrial dynamics (DRP1 BNIP3) controlled by circadian clock	C	Preclinical evidence	[77,78,79,80,81]
Animal/Preclinical	Circadian control of inflammation (NLRP3 NF- κ B IL-1 β)	C	Animal models; supported by observational human data	[44,47,70,71,72]
Animal/Preclinical	Circadian regulation of lipid metabolism and atherosclerosis	C	Preclinical; <2 moderate-quality studies	[28,40,66,72,85]
Animal/Preclinical	Cardiomyocyte circadian clock and contractile function	C	Preclinical evidence	[74,75,84,86]
Animal/Preclinical	Cardiac electrophysiology and ion channel regulation by circadian clock	C	Preclinical evidence	[51,93,99]
Animal/Preclinical	Circadian disruption (light cycle genetic) inducing insulin resistance and obesity	C	Animal studies only	[32,33,34,106,107]
Animal/Preclinical	TRE in cardiometabolic aging	C	Single preclinical study	[16,104]
Animal/Preclinical	Melatonin and cardiovascular protection	C	Limited preclinical evidence	[121,122]
Mechanistic Human	Clock gene polymorphisms and cardiometabolic risk	B	≥ 2 moderate-quality cohort studies	[9,18,100]
Mechanistic Human	Shift work / circadian disruption and metabolic syndrome	B	Multiple cohort studies; consistent findings	[5,15,112]
Mechanistic Human	Peripheral clock expression in human tissues (diurnal transcriptomics)	C	Observational; no interventional validation	[98,126,128]
Mechanistic Human	Sleep disturbance and inflammatory markers	B	≥ 2 moderate-quality studies	[48,49]
Mechanistic Human	Circadian variation in blood pressure and sodium excretion	C	Observational; limited sample sizes	[2,56,57,58]
Mechanistic Human	Circadian regulation of platelet reactivity and thrombosis	C	Preliminary human data	[114,115]
Clinical Outcome	Chronotherapy of antihypertensive drugs (bedtime vs. morning dosing)	A	≥ 2 high-quality RCTs	[59,60,116,117,118]
Clinical Outcome	TRE in humans for cardiometabolic health	B	≥ 2 moderate-quality RCTs	[103,105,127]
Clinical Outcome	Exercise timing (morning vs. evening) effects on blood pressure dipping	B	Multiple large cohort studies	[101,108,109,110]
Clinical Outcome	Melatonin supplementation for sleep / circadian adjustment in shift workers	C	Limited RCTs; <2 high-quality studies	[119,122]
Clinical Outcome	Light therapy for circadian alignment in hospitalized patients	C	Small trials; surrogate endpoints	[123,124]
Clinical Outcome	Circadian variation in cardiovascular events (MI stroke arrhythmia)	C	Limited evidence; awaiting large RCT	[50,96,97,111]

Clinical Outcome	Aspirin timing (bedtime vs. morning) effects on platelet reactivity	C	Single or small studies	[114,115]
Clinical Outcome	Coffee drinking timing and mortality	C	Observational only	[113]

Key studies of circadian-metabolic-cardiovascular aging pathways and interventions were classified into three categories (animal/preclinical, mechanistic human, clinical outcome) and rated the strength of evidence for each molecular pathway and intervention strategy (A, B, C). CLOCK circadian locomotor output cycles kaput; BMAL1 brain and muscle arnt-like protein 1; REV-ERB reverse erythroblastosis virus α and β ; PER period protein; CRY cryptochrome; SIRT1 sirtuin1; NAD nicotinamide adenine dinucleotide; PPAR α peroxisome proliferator-activated receptor α ; DRP1 dynamin-related protein 1; BNIP3 BCL2/adenovirus E1B 19 kDa interacting protein 3; NLRP3 NOD-like receptor pyrin domain-containing protein 3; NF- κ B nuclear factor- κ B; IL interleukin; TRE time-restricted eating; TRF time-restricted feeding; MI myocardial infarction.

1. Core Molecular Mechanisms: Circadian Control of Metabolic–Cardiovascular Crosstalk

Circadian rhythms are regulated by a hierarchical system where the SCN, the central clock, synchronizes peripheral clocks through neural, hormonal, and behavioral cues (for example, food intake and light exposure) [20]. The core molecular mechanism involves a transcription–translation feedback loop (TTFL): the circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like protein 1 (BMAL1) form a heterodimer that activates the transcription of period protein (PER) and cryptochrome (CRY) genes, whose products subsequently inhibit CLOCK/BMAL1 activity [21,22]. This loop regulates downstream clock-controlled genes (CCGs) involved in metabolism, inflammation, and vascular function (Fig. 1C) [23,24].

1.1 Circadian Clock System: Hierarchical Regulation

The central clock in the SCN synchronizes peripheral clocks via multiple pathways. Neural projections influence autonomic nervous system activity, while humoral signals, such as melatonin and cortisol, align tissue-specific rhythms [20]. Peripheral clocks in cardiovascular tissues (myocardium, vascular endothelium, and smooth muscle) and metabolic organs (liver and adipose tissue) maintain their own rhythms, ensuring that local physiological processes are in sync with systemic circadian cycles [10,11]. Disruptions in this hierarchical coordination, whether owing to central clock dysfunction or peripheral desynchronization, directly impact metabolic–cardiovascular homeostasis (Fig. 1B).

1.2 Key Molecular Hubs

Circadian regulation of metabolic–cardiovascular interactions centers around three key molecular hubs that connect clock genes to downstream physiological pathways. Sirtuin 1 (SIRT1), regulated by CLOCK/BMAL1, influences lipid metabolism (through peroxisome proliferator-activated receptor α [PPAR α] deacetylation) and vascular inflammation via nuclear factor kappa B inhibition. Its dysregulation can worsen insulin resistance and promote atherosclerotic lesions

[25–27]. PPAR α , activated by the CLOCK/BMAL1 heterodimer, regulates cardiac fatty acid oxidation and lipid homeostasis. Disruption of circadian rhythms can destabilize PPAR α , leading to cardiac lipotoxicity and diabetic cardiomyopathy [28]. Reverse erythroblastosis virus α (REV-ERB α), a negative regulator of the TTFL, affects hepatic insulin sensitivity (via gamma-aminobutyric acid neuron activity) and vascular inflammation (via NOD-like receptor pyrin domain-containing protein 3 [NLRP3] inflammasome inhibition). Agonists demonstrate potential benefits in cardiac remodeling but come with off-target risks and limited human data [29–31].

1.3 Pathway Crosstalk

Circadian rhythms play a crucial role in maintaining metabolic–cardiovascular homeostasis by synchronizing three interconnected pathways: insulin sensitivity, lipid metabolism, and inflammation, whose dysregulation aggravates aging-related disease. Insulin sensitivity peaks in the morning, and circadian disruptions can alter signaling pathways involving serine/threonine kinase (AKT), ribosomal protein S6 kinase beta-1, and insulin receptor substrate 1, leading to insulin resistance [32–34]. CLOCK deficiency downregulates the expression of insulin signaling genes (for example, insulin receptor and AKT2) [35], while insulin resistance negatively affects endothelial function and promotes vascular inflammation [36–38]. Genes responsible for apolipoproteins (Apo), fatty acid synthase (FASN), and microsomal triglyceride transfer protein (MTP) are regulated by circadian rhythms; their disruption potentially results in low-density lipoprotein (LDL) cholesterol accumulation and the formation of oxidized LDL (oxLDL) [39–41]. Elevated oxLDL levels can lower SIRT1, impair autophagy, and stimulate foam cell formation in atherosclerotic plaques [42,43]. Circadian rhythms also regulate inflammasome pathways (for example, NLRP3) and pro-inflammatory cytokine expression (interleukin [IL]-6 and tumor necrosis factor alpha [TNF α]) [44–46]. Systemic inflammation can disrupt circadian rhythms, creating a feedback loop that exacerbates metabolic and cardiovascular dysfunction [47]. Factors such as sleep deprivation and light-at-night increase systemic

inflammation (elevated C-reactive protein [CRP], IL-6, and TNF α levels), disrupting endothelial integrity and vascular smooth muscle cell function [12–14,48,49].

2. Cardiovascular Aging Driven by Circadian Dysregulation

Circadian disruption accelerates cardiovascular aging through various interconnected mechanisms, with age-related declines in clock function amplifying these pathological processes. Figure 3 illustrates the mechanistic link between clock dysregulation and cardiovascular aging phenotypes, highlighting the unified cascade defining circadian-driven cardiovascular aging.

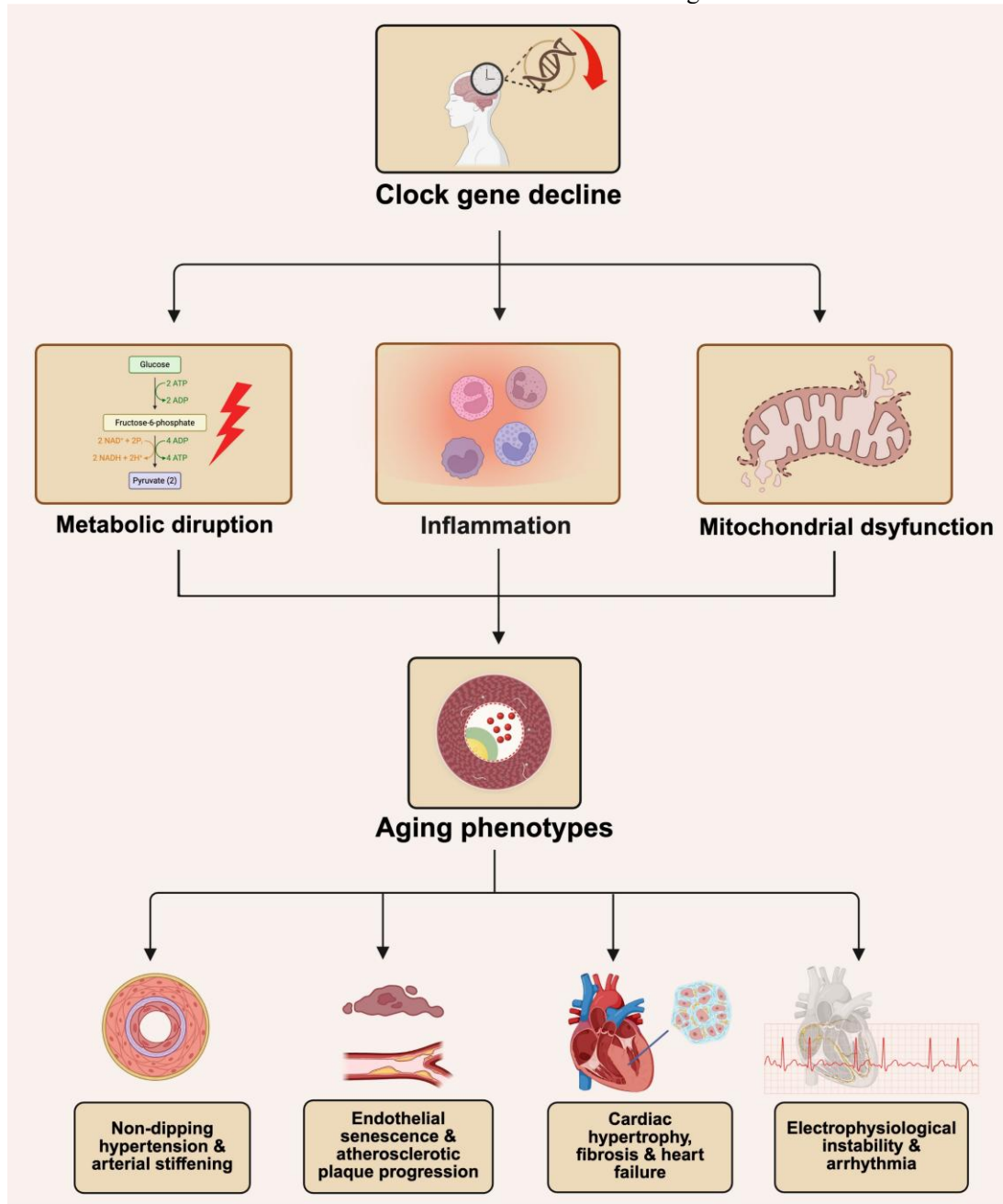


Figure 3. The integrated mechanistic link of clock dysregulation to cardiovascular aging phenotypes. Age-related decline in clock gene expression leads to circadian disruption, metabolic dysfunction, mitochondrial impairment, and chronic inflammation. These sequential and interactive changes collectively promote a range of cardiovascular aging phenotypes, including endothelial senescence, accelerated atherosclerotic plaque progression, non-dipping hypertension, arterial stiffening, cardiac hypertrophy, myocardial fibrosis, heart failure, electrophysiological instability and arrhythmias.

2.1 Blood Pressure Regulation and Arterial Stiffness

Mammalian blood pressure exhibits a distinct circadian rhythm: in diurnal species such as humans, it typically decreases by 10%–20% during nighttime sleep (the “dipping” pattern) and rises sharply in the early morning (6–10 AM), a change linked to increased sympathetic

activity and decreased parasympathetic tone [50]. Disruption of this rhythm can lead to “non-dipping hypertension” (insufficient nocturnal blood pressure decline). This condition is a significant risk factor for vascular aging, as it subjects blood vessels to prolonged high pressure, accelerating endothelial dysfunction, arterial stiffness, and atherosclerosis progression [50].

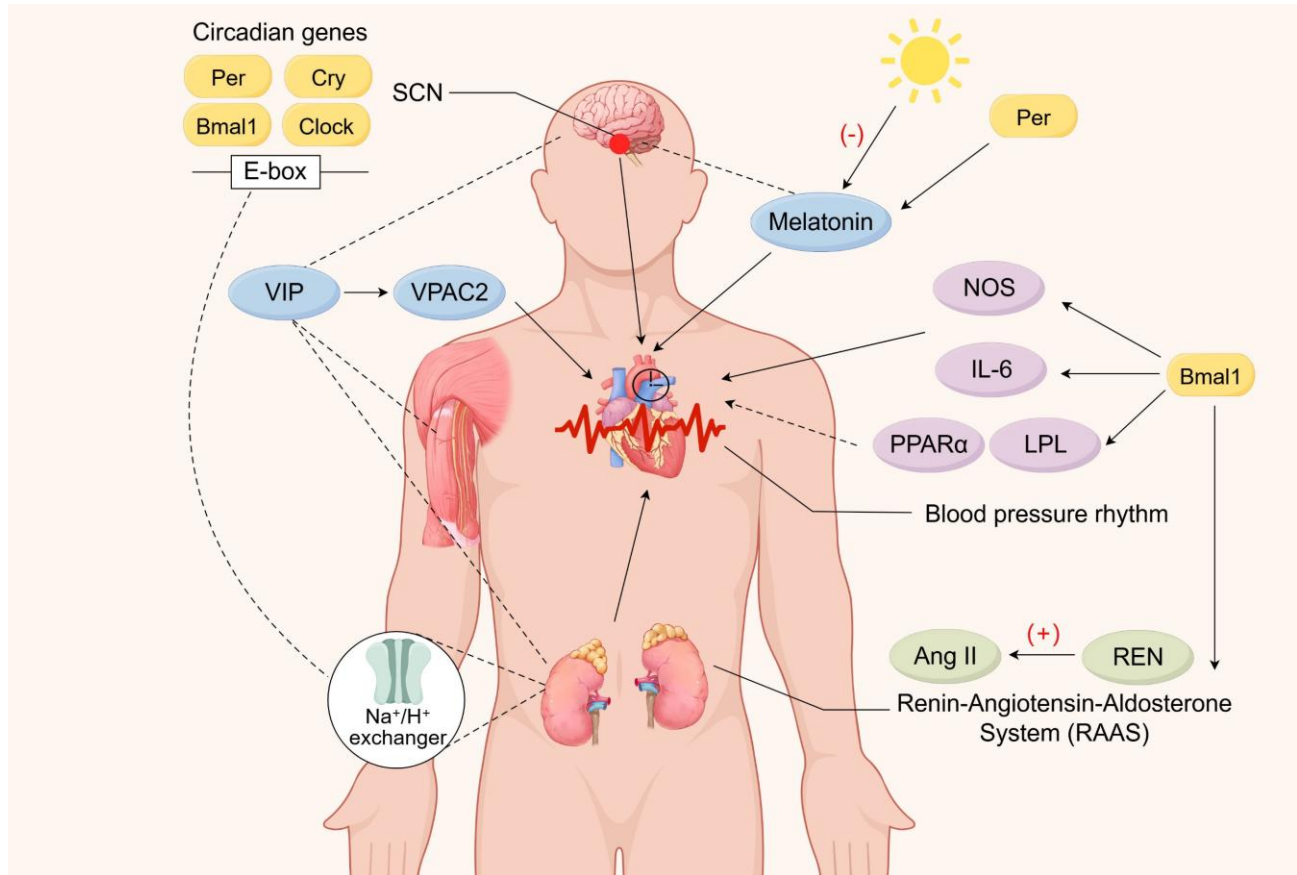


Figure 4. Factors affecting the rhythmic regulation of blood pressure. Factors affecting the rhythmic regulation of blood pressure involve complex interactions between circadian genes, hormonal signals, and physiological pathways. The central circadian clock located in the SCN regulates key genes such as *Per*, *Cry*, *Bmal1*, and *Clock*, which interact with the E-box to maintain circadian rhythms. Light exposure suppresses melatonin production, influencing downstream effects on blood pressure. Key molecular mediators such as NOS, IL-6, PPAR α , and LPL are regulated by *Bmal1*, affecting vascular tone, inflammation, and lipid metabolism. The RAAS, involving renin and angiotensin II, also plays a critical role in blood pressure modulation, with *Bmal1* influencing this pathway. Additionally, VIP and its receptor VPAC2 contribute to circadian regulation of cardiovascular function, while sodium-hydrogen (Na^+/H^+) exchangers in peripheral tissues further modulate blood pressure rhythms. These interconnected factors collectively ensure the oscillatory regulation of blood pressure, adapting to daily physiological demands. SCN suprachiasmatic nucleus; CLOCK circadian locomotor output cycles kaput; BMAL1 brain and muscle arnt-like protein 1; LPL lipoprotein lipase; PPAR α peroxisome proliferator-activated receptor α ; NOS nitric oxide synthase; IL-6 interleukin-6; LPL lipoprotein lipase; RAAS renin-angiotensin-aldosterone system; VIP vasoactive intestinal peptide; VPAC2 vasoactive intestinal peptide receptor 2.

Research has identified critical molecular pathways connecting circadian clock dysregulation to blood pressure issues. Knocking out of the core clock gene *Bmal1* in vascular endothelial and smooth muscle cells reduces mean arterial pressure in mice, emphasizing the importance of vascular clock function in blood pressure regulation [51]. Conversely, the double knockout of the

clock genes cryptochrome circadian regulator 1 and 2 (CRY1 and CRY2) leads to salt-sensitive hypertension, likely owing to disrupted sympathetic adrenal function and altered catecholamine metabolism [52,53]. Additionally, the renal Na^+/H^+ exchanger (NHE3) is regulated by the circadian clock, with its promoter's functional E-box elements activated by the CLOCK/

BMAL1 heterodimer. Disruption of NHE3 impairs sodium excretion rhythms [54-61]. The central SCN coordinates systemic blood pressure rhythms through neural and hormonal pathways, balancing sympathetic and parasympathetic activity. It secretes vasoactive intestinal peptide, crucial for synchronizing peripheral clocks, and its expression is notably reduced in individuals with essential hypertension [62,63]. In spontaneously hypertensive rats, abnormal circadian blood pressure rhythms—such as blunted nighttime dipping and shifted morning peaks—are associated with altered expression of CLOCK and BMAL1 in cardiac and vascular tissues, alongside increased activity of the renin-angiotensin system components (Fig. 4) [64]. These

findings underline that circadian blood pressure regulation deteriorates with age, raising the risk of refractory hypertension and target-organ damage.

2.2 Atherosclerosis

Atherosclerosis, a progressive vascular disorder associated with aging, is characterized by the accumulation of lipids, inflammatory cells, and fibrous tissue in arterial walls. This condition is strongly influenced by circadian dysregulation of lipid metabolism, endothelial function, and inflammation, which collectively accelerate plaque formation, instability, and vascular aging (Fig. 5).

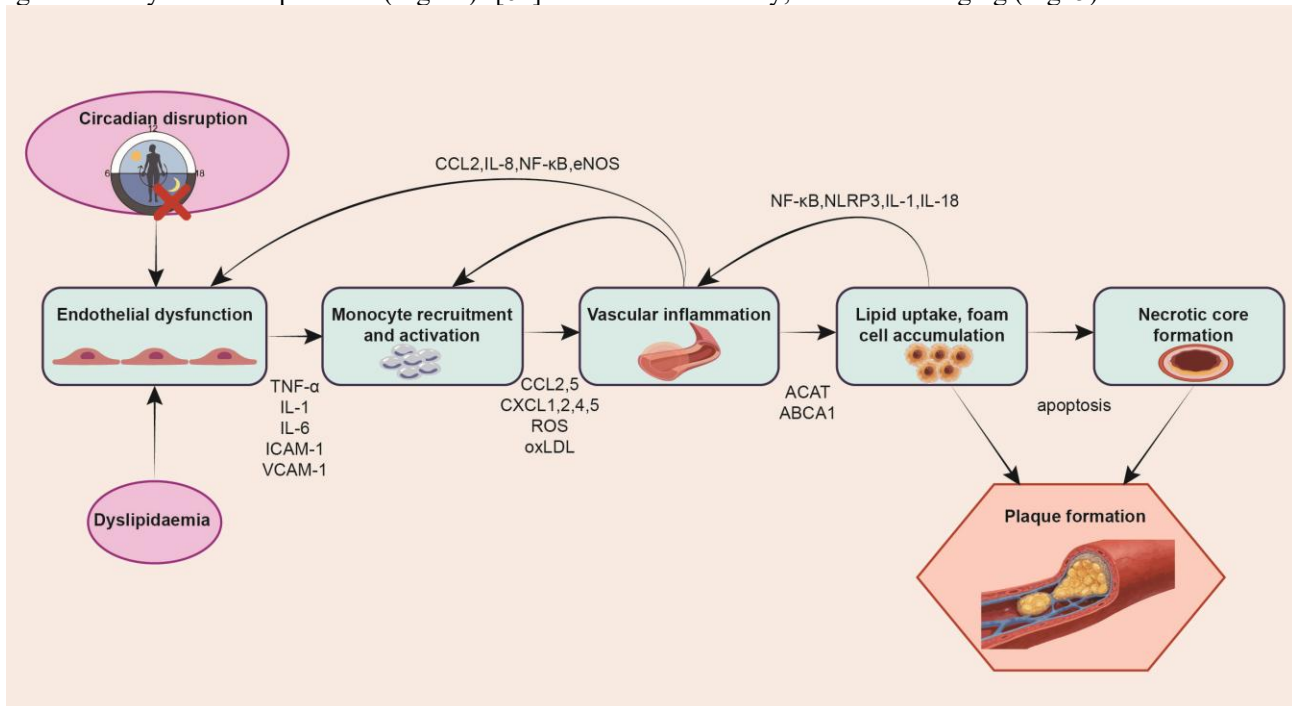


Figure 5. The role of the circadian clock in the pathogenesis of atherosclerosis. The circadian clock plays a crucial role in the pathogenesis of atherosclerosis by regulating lipid metabolism, endothelial function and vascular inflammation. Disruption of clock genes impairs NO production and increases inflammatory mediators such as IL-6, IL-1, TNF- α , and ROS, leading to endothelial dysfunction and heightened inflammation. Dysregulation of lipid metabolism pathways, contributes to elevated FFAs and oxidized LDL, exacerbating vascular inflammation. These processes converge through activation of NF- κ B signaling pathways, NLRP3 and inflammatory mediators. Macrophages internalize modified lipoproteins via dysregulated cholesterol transporters (ACAT, ABCA1) to form foam cells, whose apoptosis and sustained inflammation drive necrotic core formation and culminate in atherosclerotic plaque development. NO nitric oxide; CCL C-C motif chemokine ligand; CXCL C-X-C motif chemokine ligand; IL interleukin; ICAM intercellular adhesion molecule; VCAM vascular cell adhesion molecule; TNF- α tumor necrosis factor- α ; ROS reactive oxygen species; eNOS endothelial nitric oxide synthase; NF- κ B nuclear factor- κ B; NLRP3 NOD-like receptor family pyrin domain-containing 3; ACAT cholesterol acyltransferase; ABCA1 ATP binding cassette subfamily A member 1.

2.2.1 Dyslipidemia

In lipid metabolism, circadian clocks regulate the rhythmic expression of genes critical for cholesterol synthesis, transport, and catabolism. Core clock genes, including *CLOCK*, *BMAL1*, and *REV-ERBa*, influence the transcription of Apo, FASN, and MTP, essential for

assembling lipoproteins and maintaining plasma lipid homeostasis [39–41]. Circadian disruptions—owing to irregular sleep, shift work, or environmental light changes—negatively impact these lipid-regulating genes. For example, mice lacking the *Clock* gene exhibit elevated intestinal cholesterol absorption, decreased macrophage cholesterol efflux, and heightened accumulation of LDL

cholesterol in the vasculature [65,66]. This excess LDL is subsequently oxidized (oxLDL), triggering a pro-atherogenic response by reducing the expression of SIRT1, an anti-atherogenic deacetylase, and impairing autophagic flux in macrophages, which hinders the clearance of lipid-laden foam cells and exacerbates plaque lipid burden [42,43]. In contrast, overexpression of the *Cry1* gene in ApoE^{-/-} mice (an atherosclerotic model) considerably reduces plasma lipid levels and plaque size, accentuating the protective role of circadian lipid regulation [67].

2.2.2 Endothelial Cell Dysfunction

Circadian dysregulation also disrupts endothelial function, an early step in atherosclerosis. The vascular endothelium maintains homeostasis by regulating vasodilation, platelet aggregation, and inflammatory cell adhesion, all of which are influenced by circadian rhythms. Core clock genes in endothelial cells, such as CLOCK and BMAL1, regulate the expression of endothelial nitric oxide synthase (eNOS), which produces nitric oxide (NO), a vital vasodilator and anti-inflammatory agent [68]. Disruption of these genes impairs eNOS oscillation, as observed in *Per2* mutant mice, which exhibit reduced NO release and increased vasoconstrictor production, eliciting endothelial dysfunction and greater arterial stiffness [53]. Moreover, circadian disruption upregulates the expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in endothelial cells, fostering monocyte adhesion and migration into the subendothelial space [69]. Once within the vessel wall, these monocytes differentiate into macrophages that engulf oxLDL, contributing to foam cell formation and atherosclerotic plaques. Knocking out *Bmal1* in endothelial cells worsens barrier dysfunction by increasing the expression of chemokines such as C-C motif chemokine ligand 2 and C-X-C motif chemokine ligand 5, which accelerates monocyte recruitment and plaque initiation [70].

2.2.3 Vascular Inflammation

Inflammation is a key factor in the progression of atherosclerosis, closely regulated by circadian rhythms. Disruption of these rhythms can intensify pro-atherogenic inflammatory responses. Circadian clocks regulate the expression of inflammasome components (for example, NLRP3) and pro-inflammatory cytokines (IL-1 β , IL-6, and TNF α) in immune cells, such as macrophages in mouse models [44–46]. For instance, *in vitro* studies have demonstrated that BMAL1 deficiency in macrophages increases oxidative stress and boosts the secretion of IL-1 β , a cytokine that drives vascular smooth muscle cell

proliferation and extracellular matrix remodeling, both crucial for plaque development [71]. Sleep deprivation, a frequent cause of circadian disruption, further heightens systemic inflammation by raising plasma levels of CRP and TNF α , while increasing the number of pro-inflammatory monocytes in circulation [72]. These activated monocytes migrate to atherosclerotic plaques and release cytokines that destabilize plaques by weakening the fibrous cap. Furthermore, the clock gene REV-ERB α serves as a negative regulator of inflammation by inhibiting the TH17 cell-mediated production of IL-1 β and IL-6. REV-ERB α dysregulation eliminates this inhibitory effect, contributing to chronic vascular inflammation [45,46].

2.3 Mitochondrial Dysfunction in Cardiovascular Aging

Circadian rhythms play an indispensable role in regulating mitochondrial quality control in cardiovascular tissues. Mitochondria, which constitute approximately 30% of cardiomyocyte volume, are vital for maintaining energy homeostasis and redox balance [73,74]. Circadian systems coordinate mitophagy (through the rhythmic expression of PTEN-induced kinase 1 and BCL2 interacting protein 3) and mitochondrial dynamics (via dynamin-related protein 1 (Drp1)-mediated fission and mitofusin 1/2-mediated fusion), ensuring the removal of damaged mitochondria and adaptation to fluctuating cardiac energy demands [75–79].

Research indicates that *Bmal1* depletion disrupts the rhythmic activation of mitophagic pathways, leading to an accumulation of dysfunctional mitochondria with diminished oxidative phosphorylation efficiency and increased reactive oxygen species (ROS) production [74,79]. Additionally, abnormal Drp1 phosphorylation alters the fission–fusion balance, culminating in excessive mitochondrial fragmentation, which exacerbates ROS release and oxidative stress in vascular cells and cardiomyocytes [80,81]. ROS contributes to endothelial senescence, myocardial fibrosis, and stiffening, which are hallmark features of cardiovascular aging [16,76]. With age-related declines in circadian regulation, the progressive loss of clock-controlled mitochondrial quality control aggravates mitochondrial dysfunction, creating a feedback loop that accelerates cardiovascular aging.

2.4 Cardiac Dysfunction in Aging

Cardiomyocyte circadian rhythms play a crucial role in regulating cardiac output throughout the day. During the daytime, sympathetic nervous activity predominates, leading to increased catecholamine secretion, cardiac output, and heart rate. Conversely, at night, vagal activity takes over, attenuating peripheral vascular resistance and

cardiac output [82]. This diurnal rhythm aligns blood pressure with the body's activity cycles, safeguarding vital organs. Nonetheless, with aging, the rhythmic control of cardiac metabolism, ion channel function, and hemodynamics declines [83], resulting in cardiomyocyte hypertrophy, interstitial fibrosis, diastolic dysfunction, increased wall stress, reduced contractile reserve, and an elevated risk of heart failure. Age-related changes also encompass left ventricular diastolic stiffening, diminished β -adrenergic reserve, and heightened susceptibility to heart failure with preserved ejection fraction. Circadian dysregulation worsens these conditions by impeding calcium handling (via sarcoplasmic/endoplasmic reticulum Ca^{2+} -ATPase 2a and ryanodine receptor 2 rhythms), disrupting metabolic flexibility (reducing fatty acid oxidation oscillation), and promoting pro-fibrotic signaling (transforming growth factor beta [TGF- β]/SMAD family member 3 [Smad3]) [84]. Collectively, these clock-dependent mechanisms accelerate the transition from normal cardiac aging to pathological heart failure.

Gene knockout studies reveal that cardiomyocyte-specific deletion of *Bmal1* leads to age-dependent hypertrophic cardiomyopathy. This is characterized by increased cell size, left ventricular hypertrophy, elevated serum brain natriuretic peptide levels, and interstitial fibrosis, ultimately impairing cardiac contractile and diastolic function. In contrast, global *Bmal1* deletion results in thinning of the myocardium and loss of contractile function, resembling dilated cardiomyopathy [85,86]. Research also indicates that REV-ERB deletion promotes dilated phenotypes [87]. Furthermore, REV-ERB agonists can partially reverse hypertrophy in *Bmal1* cardiomyocyte-specific deletion mice [88], establishing a direct link between clock disruption and age-dependent cardiac phenotypes.

2.5 Cardiac Electrophysiology and Arrhythmias

As individuals age, the expression of core clock genes—such as *Bmal1*, *Clock*, and *Per2*—declines in cardiomyocytes and the autonomic nervous system [83,84]. This age-related circadian dampening disrupts the rhythmic control of ion channel genes, including the sodium and potassium channels *Scn5a* and *Kcnh2*, respectively, both regulated by circadian clock machinery at the transcriptional level [89,90]. The loss of these circadian oscillations leads to reduced electrophysiological stability, manifesting as abnormal ventricular repolarization, prolonged QT intervals, increased QT dispersion, and heightened susceptibility to atrial fibrillation (AF) and ventricular premature beats [91–93].

Genetic models can elucidate clock-dependent arrhythmogenesis. Cardiomyocyte-specific *Bmal1* knockout abolishes action potential circadian rhythms and increases pacing-induced arrhythmias, driven by mitochondrial ROS overproduction that oxidizes ion channels and impairs repolarization [74]. *Per2* overexpression enhances NO bioavailability and endothelial–electrophysiological coupling, suggesting antiarrhythmic protection through vascular–cardiac interactions [53]. Additionally, REV-ERB α regulates connexin 43 (Cx43), and age-related Cx43 loss decelerates conduction and promotes reentrant arrhythmias [45,46].

Large cohort studies confirm that long-term circadian misalignment (for example, sleep fragmentation, shift work, and jet lag) and poor sleep quality independently predict incident AF in older adults, even after adjusting for cardiovascular risk factors [94–98]. UK Biobank data indicate that irregular sleep–wake patterns increase AF risk by 26% over 7 years [97]. Older inpatients with blunted melatonin rhythms experience prolonged QT intervals and more arrhythmic events.

Aging-related atrial remodeling encompasses fibrosis, hypertrophy, and downregulation of potassium channels (Kv4.3 and Kv1.5), which impede conduction and promote reentry. Circadian dysregulation accelerates this remodeling through increased TGF- β /Smad3 signaling and decreased SIRT1 levels, preserving electrical stability [99,100].

Overall, aging hearts are more susceptible to arrhythmias owing to clock gene suppression, oxidative stress, ion channel dysregulation, and structural changes. Interventions targeting circadian pathways via behavioral strategies (for example, sleep optimization and light therapy) or clock-modulating agents (for example, REV-ERB agonists and melatonin) exhibit promise as preventive measures but require extensive large-scale clinical validation.

3. Evidence-based Clinical Interventions for Cardiovascular Aging

Circadian-based interventions utilize zeitgebers (time cues) to restore circadian balance, presenting effective strategies for alleviating cardiovascular risk (Fig. 6).

3.1 Chrononutrition: Time-restricted Eating (TRE)

TRE synchronizes food intake with circadian rhythms, enhancing metabolic and cardiovascular health by improving clock gene expression and mitigating oxidative stress [101,102]. Clinical evidence for TRE is rated B, as most studies have focused on surrogate cardiometabolic endpoints rather than direct markers of cardiovascular

aging or hard cardiovascular events. In individuals with obesity, 8–10 h TRE has proven to reduce body fat, blood pressure, and triglyceride levels [103,104]. Firefighters on 24-h shifts who practiced TRE reported improvements in blood pressure and glycated hemoglobin; however, the

TRE regimen should align with their activity–rest cycles for optimal efficacy[105]. Animal studies indicate that TRE can reverse cardiac remodeling and decrease atherosclerosis risk [106,107].

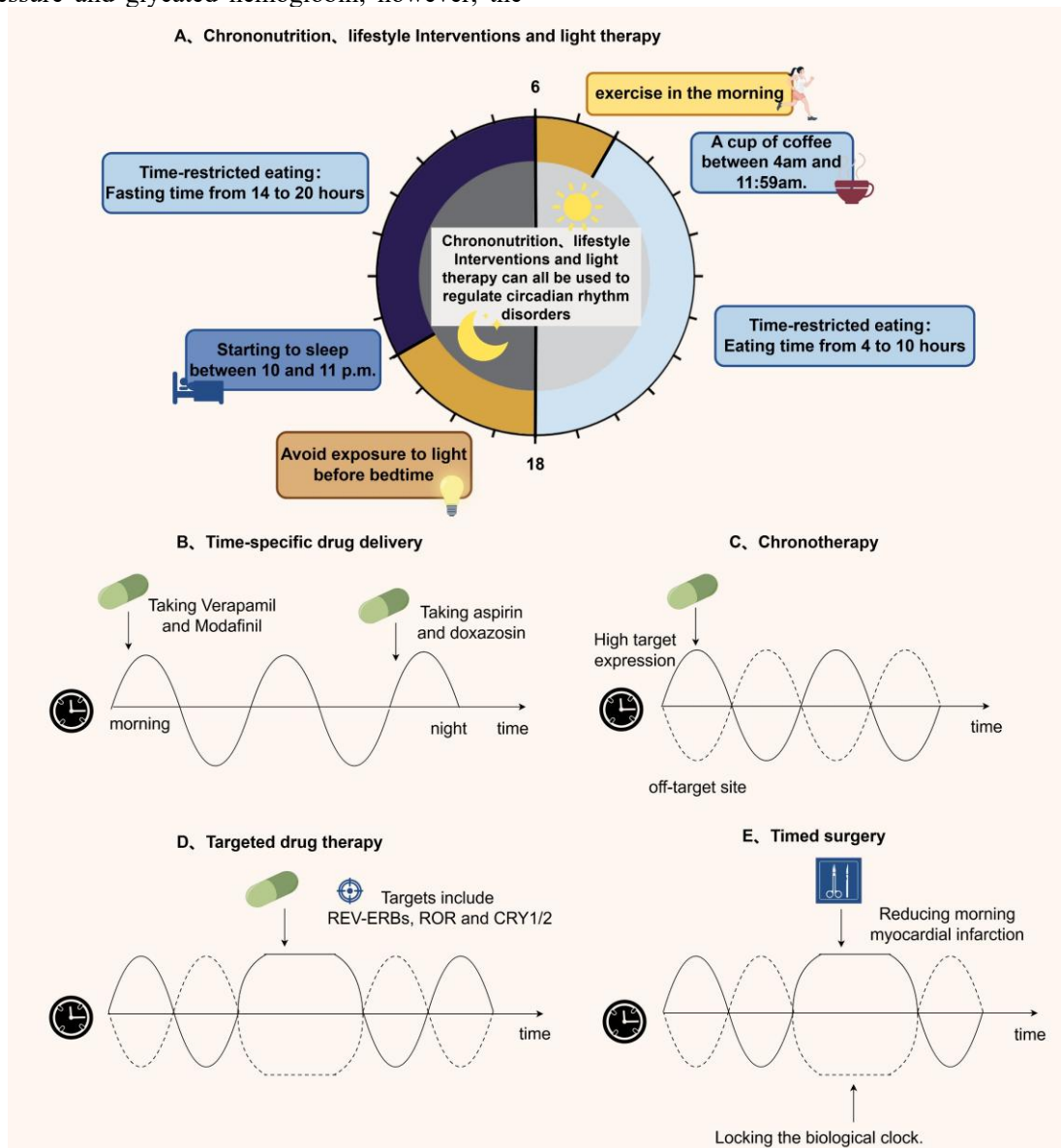


Figure 6. Interventions for restoring circadian rhythms and reducing the risk of cardiovascular diseases. A) A schematic of an ideal TRE intervention designed to promote long-term adherence by aligning the eating window with optimal sleep time and duration. Since bright light is known to inhibit the production and secretion of the sleep-promoting hormone melatonin, it is recommended to avoid bright light exposure 2 to 3 hours before habitual bedtime to improve sleep quality. Adequate sleep is known to reduce food cravings, which can support adherence to the TRE regimen. Additionally, since melatonin may attenuate glucose-induced insulin release from the pancreas, avoiding food intake right before bedtime or immediately after waking up may further enhance TRE's benefits on glucose regulation. A 10-hour eating window is illustrated as an example; Pharmacological approaches include B) Time-specific drug delivery, which times medication for maximum efficacy and minimal side effects, and C) Chronotherapy, which targets the circadian system to optimize treatment outcomes; D) Targeted drug therapy further modulates specific circadian regulators, while E) Timed surgeries align procedures with biological rhythms to lower risks, such as reducing morning myocardial infarction. These strategies harmonize lifestyle, medication, and medical interventions to support circadian health and cardiovascular protection. TRE time-restricted eating.

Nevertheless, the optimal eating window (8 h versus 10 h) and long-term efficacy in frail, older, or diabetic populations remain unvalidated [104]. While daytime 8–10 h TRE is evidence-based for middle-aged adults, its application in older adults relies on expert opinion and requires monitoring.

3.2 Lifestyle Interventions

Exercise Timing: Moderate aerobic exercise in the morning (9–11 AM) enhances blood pressure regulation in non-dipper patients with hypertension [108,109], while avoiding strenuous activity in the early morning (6–8 AM) decreases the risk of acute cardiovascular events [110]. For older patients, low-intensity morning exercise is recommended to balance cardiovascular benefits and safety.

Sleep Optimization: Initiating sleep between 10 PM and 11 PM correlates with the lowest cardiovascular risk, likely owing to increased sunlight exposure (a key zeitgeber) the next day [111]. Napping for 20–30 min during night shifts can help mitigate circadian disruption for shift workers [112].

Coffee Consumption: Morning coffee intake (4 AM–12 PM) lowers cardiovascular risk by 16% through anti-inflammatory effects, while consumption throughout the day yields no benefit [113]. Moderate morning coffee (1–3 cups/day) is advised for stable patients with cardiovascular disease.

3.3 Chronotherapy

Chronotherapy involves timing medication to align with circadian rhythms, thereby enhancing efficacy and minimizing side effects by leveraging diurnal variations in drug metabolism, target expression, and disease pathology. Bedtime dosing of low-dose aspirin targets peak platelet activity to prevent morning cardiovascular events [114], while bedtime administration of antihypertensives such as doxazosin better controls early-morning blood pressure surges [115,116]. Statins, such as atorvastatin, are more effective when administered at night, coinciding with the circadian peak of hepatic cholesterol synthesis [117]. In contrast, verapamil and modafinil are best taken in the morning to reduce daytime sleepiness [118]. Nonetheless, trials of antihypertensive chronotherapy have generated inconsistent results, and its generalizability to older, frail, or polypharmacy patients remains uncertain. Moreover, adherence challenges may limit real-world effectiveness [119].

Conventional chronotherapy is evidence-based, while clock-targeted pharmacology remains under investigation. REV-ERB agonists, such as SR9009, demonstrate benefits in cardiac remodeling induced by

pressure overload, primarily through lipid metabolism and inflammation regulation [30,31]. Conversely, the REV-ERB inhibitor SR8278 exerts protective effects against cardiac injury in preclinical models by preserving mitochondrial function and mitigating oxidative stress [120]. However, further research is necessary to clarify tissue specificity, address off-target effects, and validate the clinical applicability of these agents, particularly in aging populations where circadian dysregulation and age-related cardiovascular alterations may influence therapeutic responses.

3.4 Light Therapy

In addition to medication timing, light exposure—a potent zeitgeber of the circadian clock—along with its effect on melatonin, should be considered to optimize health and minimize adverse effects [121]. Melatonin supplementation can help restore circadian rhythms in patients experiencing circadian disruptions, thereby alleviating cardiovascular disease risk [122]. Controlled lighting systems in hospital wards may offer considerable benefits, as studies indicate that hospitalization can disrupt patients' circadian rhythms [123]. Research by Mangini et al. demonstrated that specialized glasses filtering specific wavelengths of light in the morning and evening can help restore the circadian rhythms of hospitalized patients, potentially shortening hospital stays [124]. Nevertheless, the efficacy and safety of light therapy and melatonin in older inpatients with cardiovascular disease have yet to be fully validated. Although mechanistic and pilot data support their use, routine clinical implementation cannot yet be recommended.

4. Controversies and Unresolved Questions

Despite notable advances, several critical questions remain in the field:

4.1 Cell-type Specificity of Clock Genes

Clock functions vary among endothelial cells, cardiomyocytes, and macrophages [125]. Single-cell RNA sequencing reveals cell-specific CCGs; however, their clinical relevance is yet unproven [126]. Targeted therapies are warranted to prevent off-target effects.

4.2 Optimal Parameters for Circadian-based Interventions

TRE duration, exercise timing, and light exposure lack validated age-specific protocols. Most trials exclude frail, multimorbid, or older participants [127].

4.3 Translational Gap between Preclinical and Clinical Studies

Rodents (nocturnal) and humans (diurnal) exhibit a 12-h shift in core clock gene expression [128,129], raising concerns regarding the translatability of preclinical findings. Human studies are constrained by the invasive nature of cardiac tissue sampling [130], and few clinical trials have validated circadian-based interventions in diverse populations, such as older adults, patients with diabetes, and shift workers.

4.4 Off-target Effects of Clock-modulating Drugs

While REV-ERB agonists such as SR9009 exhibit beneficial cardiac effects, non-cardiac off-target actions have also been reported [131]. Furthermore, the long-term safety of clock-targeting drugs is unclear, underlining the necessity for tissue-specific targeting and rigorous clinical testing.

4.5 Real-world Translational Barriers

Translating circadian-based interventions into clinical practice to address cardiovascular aging presents several challenges: (1) the limited availability of circadian phenotyping tools in routine clinical settings (for example, objective measurements of circadian phase), (2) difficulties in assessing circadian rhythms in older adults (for example, fragmented sleep and comorbidities obscuring rhythm patterns), (3) adherence to behavioral circadian interventions (for example, TRE and exercise timing) among older adults with functional limitations, (4) variable work schedules and social obligations (for example, shift work and caregiving) that disrupt zeitgeber alignment, (5) the complexities of implementing circadian interventions for older adults with multiple health conditions and polypharmacy, and (6) insufficient clinician education and training in circadian medicine.

CONCLUSION AND FUTURE PERSPECTIVE

Circadian rhythms play a crucial role in maintaining metabolic and cardiovascular health. The decline in clock function associated with aging contributes to metabolic dysfunction, inflammation, mitochondrial damage, and cardiovascular deterioration. Key regulatory factors include SIRT1, PPAR α , and REV-ERB α .

While circadian-based interventions exhibit potential, they are not yet ready for widespread clinical use. Evidence corroborates TRE, standard chronotherapy, and the timing of sleep and exercise; however, most studies involve short durations and select populations. Validation in older, frail, and multimorbid patients is imperative.

Future efforts should focus on (1) conducting large, long-term randomized controlled trials in aging populations; (2) developing validated circadian phenotyping tools for clinical application (for example, monitoring sleep–wake cycles, blood pressure rhythms, and chronotype); (3) creating personalized protocols that consider age, chronotype, frailty, and comorbidities (for example, shorter TRE windows for frail older adults and adjusted chronotherapy timing for evening-type hypertensives); (4) developing tissue-specific therapies targeting circadian clocks; (5) implementing strategies to address adherence and scheduling challenges in real-world settings.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Author contributions

Conceptualization, J.W., and T.C.; formal analysis, J.W.; investigation, J.W. and Q.X.; resources, T.C.; writing—original draft preparation, J. W. and Q.X.; writing—review and editing, T.C. and X.H.; project administration, T.C. and X.H.; funding acquisition, T.C. and X.H. All authors have read and agreed to the published version of the manuscript.

References

- [1] Pittendrigh CS (1960). Circadian rhythms and the circadian organization of living systems. *Cold Spring Harb Symp Quant Biol*, 25:159–84.
- [2] Millar-Craig MW, Bishop CN, Raftery EB (1978). Circadian variation of blood-pressure. *Lancet*, 1:795–7.
- [3] Hall JC (1990). Genetics of circadian rhythms. *Annu Rev Genet*, 24:659–97.
- [4] Takahashi JS (1991). Circadian rhythms: from gene expression to behavior. *Curr Opin Neurobiol*, 1:556–61.
- [5] Aronson D (2001). Impaired modulation of circadian rhythms in patients with diabetes mellitus: a risk factor for cardiac thrombotic events? *Chronobiol Int*, 18:109–21.
- [6] Sowers JR (2001). Update on the cardiometabolic syndrome. *Clin Cornerstone*, 4:17–23.

- [7] Antoch MP, Kondratov RV, Takahashi JS (2005). Circadian clock genes as modulators of sensitivity to genotoxic stress. *Cell Cycle*, 4:901–7.
- [8] Bass J, Takahashi JS (2010). Circadian integration of metabolism and energetics. *Science*, 330:1349–54.
- [9] Piggins HD (2002). Human clock genes. *Ann Med*, 34:394–400.
- [10] Liu S, Cai Y, Sothorn RB, Guan Y, Chan P (2007). Chronobiological analysis of circadian patterns in transcription of seven key clock genes in six peripheral tissues in mice. *Chronobiol Int*, 24:793–820.
- [11] Mohawk JA, Green CB, Takahashi JS (2012). Central and peripheral circadian clocks in mammals. *Annu Rev Neurosci*, 35:445–62.
- [12] Chen Z, Xiong Z-F, Liu X (2021). Research progress on the interaction between circadian clock and early vascular aging. *Exp Gerontol*, 146:111241.
- [13] Adrover JM, Del Fresno C, Crainiciuc G, Cuartero MI, Casanova-Acebes M, Weiss LA, et al. (2019). A Neutrophil Timer Coordinates Immune Defense and Vascular Protection. *Immunity*, 50:390-402.e10.
- [14] Huang H, Li Z, Ruan Y, Feng W, Chen J, Li X, et al. (2020). Circadian rhythm disorder: a potential inducer of vascular calcification? *J Physiol Biochem*, 76:513–24.
- [15] Rahman A, Hasan AU, Nishiyama A, Kobori H (2018). Altered Circadian Timing System-Mediated Non-Dipping Pattern of Blood Pressure and Associated Cardiovascular Disorders in Metabolic and Kidney Diseases. *Int J Mol Sci*, 19:400.
- [16] Roth JR, Varshney S, de Moraes RCM, Melkani GC (2023). Circadian-mediated regulation of cardiometabolic disorders and aging with time-restricted feeding. *Obesity*, 31 Suppl 1:40–9.
- [17] Nordholm A, Egstrand S, Gravesen E, Mace ML, Morevati M, Olgaard K, et al. (2019). Circadian rhythm of activin A and related parameters of mineral metabolism in normal and uremic rats. *Pflugers Arch*, 471:1079–94.
- [18] Yan L, Chen J, Li F, Chen Y, Mei Z, Chen L (2023). Circadian Rhythm and the Risk of Cardiovascular Diseases: Genetic Evidence. *Aging Dis*, 15:2328–30.
- [19] Carpenter BJ, Dierickx P (2022). Circadian cardiac NAD⁺ metabolism, from transcriptional regulation to healthy aging. *Am J Physiol Cell Physiol*, 323:C1168–76.
- [20] Lu Q, Kim JY (2022). Mammalian circadian networks mediated by the suprachiasmatic nucleus. *FEBS J*, 289:6589–604.
- [21] Brancaccio M, Edwards MD, Patton AP, Smyllie NJ, Chesham JE, Maywood ES, et al. (2019). Cell-autonomous clock of astrocytes drives circadian behavior in mammals. *Science*, 363:187–92.
- [22] Patton AP, Smyllie NJ, Chesham JE, Hastings MH (2022). Astrocytes Sustain Circadian Oscillation and Bidirectionally Determine Circadian Period, But Do Not Regulate Circadian Phase in the Suprachiasmatic Nucleus. *J Neurosci Off J Soc Neurosci*, 42:5522–37.
- [23] Finger A-M, Kramer A (2021). Peripheral clocks tick independently of their master. *Genes Dev*, 35:304–6.
- [24] Sinturel F, Gos P, Petrenko V, Hagedorn C, Kreppel F, Storch K-F, et al. (2021). Circadian hepatocyte clocks keep synchrony in the absence of a master pacemaker in the suprachiasmatic nucleus or other extrahepatic clocks. *Genes Dev*, 35:329–34.
- [25] Zhou B, Zhang Y, Zhang F, Xia Y, Liu J, Huang R, et al. (2014). CLOCK/BMAL1 regulates circadian change of mouse hepatic insulin sensitivity by SIRT1. *Hepatology*, 59:2196–206.
- [26] Chen YX, Zhang M, Cai Y, Zhao Q, Dai W (2015). The Sirt1 activator SRT1720 attenuates angiotensin II-induced atherosclerosis in apoE^{-/-} mice through inhibiting vascular inflammatory response. *Biochem Biophys Res Commun*, 465:732–8.
- [27] Miranda MX, van Tits LJ, Lohmann C, Arsiwala T, Winnik S, Tailleur A, et al. (2015). The Sirt1 activator SRT3025 provides atheroprotection in ApoE^{-/-} mice by reducing hepatic Pcsk9 secretion and enhancing Ldlr expression. *Eur Heart J*, 36:51–9.
- [28] Oishi K, Shirai H, Ishida N (2005). CLOCK is involved in the circadian transactivation of peroxisome-proliferator-activated receptor alpha (PPARalpha) in mice. *Biochem J*, 386:575–81.
- [29] Ding G, Li X, Hou X, Zhou W, Gong Y, Liu F, et al. (2021). REV-ERB in GABAergic neurons controls diurnal hepatic insulin sensitivity. *Nature*, 592:763–7.
- [30] Li H, Song S, Tien C-L, Qi L, Graves A, Nasiotis E, et al. (2021). SR9009 improves heart function after pressure overload independent of cardiac REV-ERB. *Front Cardiovasc Med*, 9:952114.
- [31] Murray MH, Valfort AC, Koelblen T, Ronin C, Ciesielski F, Chatterjee A, et al. (2022). Structural basis of synthetic agonist activation of the nuclear receptor REV-ERB. *Nat Commun*, 13:7131.
- [32] Shi S, Ansari TS, McGuinness OP, Wasserman DH, Johnson CH (2013). Circadian disruption leads to insulin resistance and obesity. *Curr Biol CB*, 23:372–81.
- [33] Her TK, Li J, Lin H, Liu D, Root KM, Regal JF, et al. (2024). Circadian Disruption across Lifespan Impairs Glucose Homeostasis and Insulin Sensitivity in Adult Mice. *Metabolites*, 14:126.
- [34] Skinner NJ, Rizwan MZ, Grattan DR, Tups A (2019). Chronic Light Cycle Disruption Alters Central Insulin and Leptin Signaling as well as Metabolic Markers in Male Mice. *Endocrinology*, 160:2257–70.
- [35] Marcheva B, Ramsey KM, Buhr ED, Kobayashi Y, Su H, Ko CH, et al. (2010). Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature*, 466:627–31.
- [36] Peng Z, Tan Y, Zou X, Zhang X (2024). Circadian rhythm in hypertension: Bibliometrics and knowledge mapping from 1990 to 2022. *Chronobiol Int*, 41:971–86.
- [37] Costello HM, Gumz ML (2021). Circadian Rhythm, Clock Genes, and Hypertension: Recent Advances in Hypertension. *Hypertension*, 78(5):1185-1196.
- [38] Lemmer B, Oster H (2018). The Role of Circadian Rhythms in the Hypertension of Diabetes Mellitus and the Metabolic Syndrome. *Curr Hypertens Rep*, 20:43.

- [39] Petrenko V, Sinturel F, Riezman H, Dibner C (2023). Lipid metabolism around the body clocks. *Prog Lipid Res*, 91:101235.
- [40] Hussain MM, Pan X (2015). Circadian regulators of intestinal lipid absorption. *J Lipid Res*, 56:761–70.
- [41] Lee CH, Murrell CE, Chu A, Pan X (2023). Circadian Regulation of Apolipoproteins in the Brain: Implications in Lipid Metabolism and Disease. *Int J Mol Sci*, 24:17415.
- [42] Yang J, Lin X, Wang L, Sun T, Zhao Q, Ma Q, et al. (2020). LncRNA MALAT1 Enhances ox-LDL-Induced Autophagy through the SIRT1/MAPK/NF- κ B Pathway in Macrophages. *Curr Vasc Pharmacol*, 18:652–62.
- [43] Jin X, Fu W, Zhou J, Shuai N, Yang Y, Wang B (2021). Oxymatrine attenuates oxidized low-density lipoprotein-induced HUVEC injury by inhibiting NLRP3 inflammasome-mediated pyroptosis via the activation of the SIRT1/Nrf2 signaling pathway. *Int J Mol Med*, 48:187.
- [44] Pourcet B, Duez H (2020). Circadian Control of Inflammasome Pathways: Implications for Circadian Medicine. *Front Immunol*, 11:1630.
- [45] Gibbs JE, Blaikley J, Beesley S, Matthews L, Simpson KD, Boyce SH, et al. (2012). The nuclear receptor REV-ERB α mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proc Natl Acad Sci U S A*, 109:582–7.
- [46] Hong H, Cheung YM, Cao X, Wu Y, Li C, Tian XY (2021). REV-ERB α agonist SR9009 suppresses IL-1 β production in macrophages through BMAL1-dependent inhibition of inflammasome. *Biochem Pharmacol*, 192:114701.
- [47] Cheng W-Y, Chan P-L, Ong H-Y, Wong K-H, Chang RC-C (2024). Systemic Inflammation Disrupts Circadian Rhythms and Diurnal Neuroimmune Dynamics. *Int J Mol Sci*, 25:7458.
- [48] Irwin MR, Olmstead R, Carroll JE (2016). Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol Psychiatry*, 80:40–52.
- [49] Xu Y-X, Shen Y-T, Li J, Ding W-Q, Wan Y-H, Su P-Y, et al. (2024). Real-ambient bedroom light at night increases systemic inflammation and disrupts circadian rhythm of inflammatory markers. *Ecotoxicol Environ Saf*, 281:116590.
- [50] Reavey M, Saner H, Paccaud F, Marques-Vidal P (2013). Exploring the periodicity of cardiovascular events in Switzerland: variation in deaths and hospitalizations across seasons, day of the week and hour of the day. *Int J Cardiol*, 168:2195–200.
- [51] Anea CB, Ali MI, Osmond JM, Sullivan JC, Stepp DW, Merloiu AM, et al. (2010). Matrix metalloproteinase 2 and 9 dysfunction underlie vascular stiffness in circadian clock mutant mice. *Arterioscler Thromb Vasc Biol*, 30(12):2535–2543.
- [52] Masuki S, Todo T, Nakano Y, Okamura H, Nose H (2005). Reduced alpha-adrenoceptor responsiveness and enhanced baroreflex sensitivity in Cry-deficient mice lacking a biological clock. *J Physiol*, 566:213–24.
- [53] Viswambharan H, Carvas JM, Antic V, Marecic A, Jud C, Zaugg CE, et al. (2007). Mutation of the circadian clock gene *Per2* alters vascular endothelial function. *Circulation*, 115:2188–95.
- [54] Saifur Rohman M, Emoto N, Nonaka H, Okura R, Nishimura M, Yagita K, et al. (2005). Circadian clock genes directly regulate expression of the Na(+)/H(+) exchanger NHE3 in the kidney. *Kidney Int*, 67:1410–9.
- [55] Wei N, Gumz ML, Layton AT (2018). Predicted effect of circadian clock modulation of NHE3 of a proximal tubule cell on sodium transport. *Am J Physiol Renal Physiol*, 315:F665–76.
- [56] Firsov D, Bonny O (2018). Circadian rhythms and the kidney. *Nat Rev Nephrol*, 14(10):626–635.
- [57] Zhang J, Rao J, Liu M, Zhou W, Li Y, Wu J, et al. (2020). Abnormal circadian rhythm of urinary sodium excretion correlates closely with hypertension and target organ damage in Chinese patients with CKD. *Int J Med Sci*, 17:702–11.
- [58] Zhang D, Pollock DM (2020). Diurnal Regulation of Renal Electrolyte Excretion: The Role of Paracrine Factors. *Annu Rev Physiol*, 82:343–363.
- [59] Yan P, Luo Y, Zhang J, Liu H, Chen J, Wang J, et al. (2023). Effect of administration of low-dose irbesartan and hydrochlorothiazide combined with levamlodipine at different times on the circadian rhythm of blood pressure and the levels of MMPs and TIMPs in non-dipper patients with grade 1 and 2 hypertension. *J Clin Hypertens*, 25:137–45.
- [60] Fukuda M, Kimura G (2006). Pathophysiology of antihypertensive therapy with diuretics. *Hypertens Res Off J Jpn Soc Hypertens*, 29:645–53.
- [61] Goto N, Uchida K, Morozumi K, Ueki T, Matsuoka S, Katayama A, et al. (2005). Circadian blood pressure rhythm is disturbed by nephrectomy. *Hypertens Res Off J Jpn Soc Hypertens*, 28:301–6.
- [62] Goncharuk VD, van Heerikhuizen J, Dai JP, Swaab DF, Buijs RM (2001). Neuropeptide changes in the suprachiasmatic nucleus in primary hypertension indicate functional impairment of the biological clock. *J Comp Neurol*, 431(3):320–330.
- [63] Aton SJ, Colwell CS, Harmar AJ, Waschek J, Herzog ED (2005). Vasoactive intestinal polypeptide mediates circadian rhythmicity and synchrony in mammalian clock neurons. *Nat Neurosci*, 8:476–83.
- [64] Naito Y, Tsujino T, Fujioka Y, Ohyanagi M, Iwasaki T (2002). Augmented diurnal variations of the cardiac renin-angiotensin system in hypertensive rats. *Hypertension*, 40:827–33.
- [65] Tang H, Zhu M, Zhao G, Fu W, Shi Z, Ding Y, et al. (2018). Loss of CLOCK under high glucose upregulates ROCK1-mediated endothelial to mesenchymal transition and aggravates plaque vulnerability. *Atherosclerosis*, 275:58–67.
- [66] Pan X, Jiang X-C, Hussain MM (2013). Impaired cholesterol metabolism and enhanced atherosclerosis in clock mutant mice. *Circulation*, 128:1758–69.
- [67] Yang L, Chu Y, Wang L, Wang Y, Zhao X, He W, et al. (2015). Overexpression of CRY1 protects against the

- development of atherosclerosis via the TLR/NF- κ B pathway. *Int Immunopharmacol*, 28:525–30.
- [68] Rodrigo GC, Herbert KE (2018). Regulation of vascular function and blood pressure by circadian variation in redox signalling. *Free Radic Biol Med*, 119:115–20.
- [69] Gao Y, Meng D, Sun N, Zhu Z, Zhao R, Lu C, et al. (2014). Clock upregulates intercellular adhesion molecule-1 expression and promotes mononuclear cells adhesion to endothelial cells. *Biochem Biophys Res Commun*, 443:586–91.
- [70] Gibbs J, Ince L, Matthews L, Mei J, Bell T, Yang N, et al. (2014). An epithelial circadian clock controls pulmonary inflammation and glucocorticoid action. *Nat Med*, 20:919–26.
- [71] Early JO, Menon D, Wyse CA, Cervantes-Silva MP, Zaslona Z, Carroll RG, et al. (2018). Circadian clock protein BMAL1 regulates IL-1 β in macrophages via NRF2. *Proc Natl Acad Sci U S A*, 115:E8460–8.
- [72] McAlpine CS, Kiss MG, Rattik S, He S, Vassalli A, Valet C, et al. (2019). Sleep modulates haematopoiesis and protects against atherosclerosis. *Nature*, 566:383–7.
- [73] El'darov ChM, Vays VB, Vangeli IM, Kolosova NG, Bakeeva LE (2015). Morphometric Examination of Mitochondrial Ultrastructure in Aging Cardiomyocytes. *Biochemistry (Mosc)*, 80(5):604–609.
- [74] Young ME, Brewer RA, Peliciari-Garcia RA, Collins HE, He L, Birky TL, et al. (2014). Cardiomyocyte-specific BMAL1 plays critical roles in metabolism, signaling, and maintenance of contractile function of the heart. *J Biol Rhythms*, 29:257–76.
- [75] McGinnis GR, Tang Y, Brewer RA, Brahma MK, Stanley HL, Shanmugam G, et al. (2017). Genetic disruption of the cardiomyocyte circadian clock differentially influences insulin-mediated processes in the heart. *J Mol Cell Cardiol*, 110:80–95.
- [76] Ma D, Panda S, Lin JD (2011). Temporal orchestration of circadian autophagy rhythm by C/EBP β . *EMBO J*, 30:4642–51.
- [77] Jin J-Y, Wei X-X, Zhi X-L, Wang X-H, Meng D (2021). Drp1-dependent mitochondrial fission in cardiovascular disease. *Acta Pharmacol Sin*, 42:655–64.
- [78] Kageyama Y, Hoshijima M, Seo K, Bedja D, Sysa-Shah P, Andrabi SA, et al. (2014). Parkin-independent mitophagy requires Drp1 and maintains the integrity of mammalian heart and brain. *EMBO J*, 33:2798–813.
- [79] Jacobi D, Liu S, Burkewitz K, Kory N, Knudsen NH, Alexander RK, et al. (2015). Hepatic Bmal1 Regulates Rhythmic Mitochondrial Dynamics and Promotes Metabolic Fitness. *Cell Metab*, 22:709–20.
- [80] Schmitt K, Grimm A, Dallmann R, Oettinghaus B, Restelli LM, Witzig M, et al. (2018). Circadian Control of DRP1 Activity Regulates Mitochondrial Dynamics and Bioenergetics. *Cell Metab*, 27:657–666.e5.
- [81] Li E, Li X, Huang J, Xu C, Liang Q, Ren K, et al. (2020). BMAL1 regulates mitochondrial fission and mitophagy through mitochondrial protein BNIP3 and is critical in the development of dilated cardiomyopathy. *Protein Cell*, 11:661–79.
- [82] El Jamal N, Lordan R, Teegarden SL, Grosser T, FitzGerald G (2023). The Circadian Biology of Heart Failure. *Circ Res*, 132:223–37.
- [83] Bettadapura SS, Todd WD, McGinnis GR, Bruns DR (2025). Circadian biology of cardiac aging. *J Mol Cell Cardiol*, 199:95–103.
- [84] Martino TA, Young ME (2015). Influence of the cardiomyocyte circadian clock on cardiac physiology and pathophysiology. *J Biol Rhythms*, 30:183–205.
- [85] Pan X, Mota S, Zhang B (2020). Circadian Clock Regulation on Lipid Metabolism and Metabolic Diseases. *Adv Exp Med Biol*, 1276:53–66.
- [86] Ingle KA, Kain V, Goel M, Prabhu SD, Young ME, Halade GV (2015). Cardiomyocyte-specific Bmal1 deletion in mice triggers diastolic dysfunction, extracellular matrix response, and impaired resolution of inflammation. *Am J Physiol Heart Circ Physiol*, 309:H1827–1836.
- [87] Mia S, Kane MS, Latimer MN, Reitz CJ, Sonkar R, Benavides GA, et al. (2020). Differential effects of REV-ERB α/β agonism on cardiac gene expression, metabolism, and contractile function in a mouse model of circadian disruption. *Am J Physiol Heart Circ Physiol*, 318:H1487–508.
- [88] Mazzocchi G, Cai Y, Liu S, Francavilla M, Giuliani F, Piepoli A, et al. (2012). REV-ERB α and the clock gene machinery in mouse peripheral tissues: a possible role as a synchronizing hinge. *J Biol Regul Homeost Agents*, 26:265–76.
- [89] Vicent L, Martínez-Sellés M (2021). Circadian rhythms, cardiac arrhythmias and sudden death. *Front Biosci*, 26:1305–11.
- [90] Schroder EA, Ono M, Johnson SR, Rozmus ER, Burgess DE, Esser KA, et al. (2022). The role of the cardiomyocyte circadian clocks in ion channel regulation and cardiac electrophysiology. *J Physiol*, 600:2037–48.
- [91] Delisle BP, Prabhat A, Burgess DE, Ono M, Esser KA, Schroder EA (2024). Circadian Regulation of Cardiac Arrhythmias and Electrophysiology. *Circ Res*, 134(6):659–674.
- [92] Durgan DJ, Trexler NA, Egbejimi O, McElfresh TA, Suk HY, Petterson LE, et al. (2006). The circadian clock within the cardiomyocyte is essential for responsiveness of the heart to fatty acids. *J Biol Chem*, 281:24254–69.
- [93] Hayter EA, Wehrens SMT, Van Dongen HPA, Stangherlin A, Gaddameedhi S, Crooks E, et al. (2021). Distinct circadian mechanisms govern cardiac rhythms and susceptibility to arrhythmia. *Nat Commun*, 12:2472.
- [94] Lu Y, Sun Y, Cai L, Yu B, Wang Y, Tan X, et al. (2025). Non-traditional risk factors for atrial fibrillation: epidemiology, mechanisms, and strategies. *Eur Heart J*, 46:784–804.
- [95] Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, et al. (2022). Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. *Circulation*, 146:e18–43.

- [96] Bedford JP, Redfern O, Johnson A, Rajappan K, Watkinson PJ (2022). Circadian variation in new-onset atrial fibrillation in patients in ICUs. *J Crit Care*, 67:1–2.
- [97] Yang L, Feng H, Ai S, Liu Y, Lei B, Chen J, et al. (2023). Association of accelerometer-derived circadian abnormalities and genetic risk with incidence of atrial fibrillation. *NPJ Digit Med*, 6:31.
- [98] Chen Y-L, Chuang J-H, Wang H-T, Chen H-C, Liu W-H, Yang M-Y (2021). Altered Expression of Circadian Clock Genes in Patients with Atrial Fibrillation Is Associated with Atrial High-Rate Episodes and Left Atrial Remodeling. *Diagnostics*, 1:90.
- [99] Schroder EA, Burgess DE, Zhang X, Lefta M, Smith JL, Patwardhan A, et al. (2015). The cardiomyocyte molecular clock regulates the circadian expression of *Kcnh2* and contributes to ventricular repolarization. *Heart Rhythm*, 12:1306–14.
- [100] Alamanca L, Gobet C, Naef F (2023). Sex-dimorphic and age-dependent organization of 24-hour gene expression rhythms in humans. *Science*, 379:478–83.
- [101] Gabriel BM, Zierath JR (2019). Circadian rhythms and exercise - re-setting the clock in metabolic disease. *Nat Rev Endocrinol*, 15:197–206.
- [102] Checa-Ros A, D'Marco L (2022). Role of Omega-3 Fatty Acids as Non-Photoc Zeitgebers and Circadian Clock Synchronizers. *Int J Mol Sci*, 23:12162.
- [103] St-Onge M-P, Ard J, Baskin ML, Chiuve SE, Johnson HM, Kris-Etherton P, et al. (2017). Meal Timing and Frequency: Implications for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association. *Circulation*, 135:e96–121.
- [104] Ezpeleta M, Cienfuegos S, Lin S, Pavlou V, Gabel K, Tussing-Humphreys L, et al. (2024). Time-restricted eating: Watching the clock to treat obesity. *Cell Metab*, 36:301–14.
- [105] Manoogian ENC, Zadourian A, Lo HC, Gutierrez NR, Shoghi A, Rosander A, et al. (2022). Feasibility of time-restricted eating and impacts on cardiometabolic health in 24-h shift workers: The Healthy Heroes randomized control trial. *Cell Metab*, 34:1442–1456.e7.
- [106] Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshi C, Kobayashi Y, et al. (2007). High-fat diet disrupts behavioral and molecular circadian rhythms in mice. *Cell Metab*, 6:414–21.
- [107] Hsieh M-C, Yang S-C, Tseng H-L, Hwang L-L, Chen C-T, Shieh K-R (2010). Abnormal expressions of circadian-clock and circadian clock-controlled genes in the livers and kidneys of long-term, high-fat-diet-treated mice. *Int J Obes*, 34:227–39.
- [108] Ling C, Diaz KM, Kretzschmar J, Feairheller DL, Sturgeon KM, Perkins A, et al. (2014). Chronic aerobic exercise improves blood pressure dipping status in African American nondippers. *Blood Press Monit*, 19:353–8.
- [109] de Brito LC, Rezende RA, da Silva Junior ND, Tinucci T, Casarini DE, Cipolla-Neto J, et al. (2015). Post-Exercise Hypotension and Its Mechanisms Differ after Morning and Evening Exercise: A Randomized Crossover Study. *PloS One*, 10:e0132458.
- [110] Pedersen BK, Saltin B (2015). Exercise as medicine-evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*, 25 Suppl 3:1–72.
- [111] Nikbakhtian S, Reed AB, Obika BD, Morelli D, Cunningham AC, Aral M, et al. (2021). Accelerometer-derived sleep onset timing and cardiovascular disease incidence: a UK Biobank cohort study. *Eur Heart J Digit Health*, 2:658–66.
- [112] Kecklund G, Axelsson J (2016). Health consequences of shift work and insufficient sleep. *BMJ*, 355:i5210.
- [113] Wang X, Ma H, Sun Q, Li J, Heianza Y, Van Dam RM, et al. (2025). Coffee drinking timing and mortality in US adults. *Eur Heart J*, 46:749–59.
- [114] Bonten TN, Saris A, van Oostrom MJ, Snoep JD, Rosendaal FR, Zwaginga J, et al. (2014). Effect of aspirin intake at bedtime versus on awakening on circadian rhythm of platelet reactivity. A randomised cross-over trial. *Thromb Haemost*, 112:1209–18.
- [115] Bonten TN, Snoep JD, Assendelft WJJ, Zwaginga JJ, Eikenboom J, Huisman MV, et al. (2015). Time-dependent effects of aspirin on blood pressure and morning platelet reactivity: a randomized cross-over trial. *Hypertension*, 65:743–50.
- [116] Haghayegh S, Smolensky MH, Khoshnevis S, Hermida RC, Castriotta RJ, Diller KR (2021). The Circadian Rhythm of Thermoregulation Modulates both the Sleep/Wake Cycle and 24 h Pattern of Arterial Blood Pressure. *Compr Physiol*, 11:2645–58.
- [117] Festus ID, Spielberg J, Young ME, Cain S, Khoshnevis S, Smolensky MH, et al. (2024). Pioneering new frontiers in circadian medicine chronotherapies for cardiovascular health. *Trends Endocrinol Metab*, 35:607–23.
- [118] Smolensky MH, Hermida RC, Geng Y-J (2021). Chronotherapy of cardiac and vascular disease: timing medications to circadian rhythms to optimize treatment effects and outcomes. *Curr Opin Pharmacol*, 57:41–8.
- [119] Liira J, Verbeek JH, Costa G, Driscoll TR, Sallinen M, Isotalo LK, et al. (2014). Pharmacological interventions for sleepiness and sleep disturbances caused by shift work. *Cochrane Database Syst Rev*, 2014:CD009776.
- [120] Wang S, Li F, Lin Y, Wu B (2020). Targeting REV-ERB α for therapeutic purposes: promises and challenges. *Theranostics*, 10:4168–82.
- [121] Claustrat B, Leston J (2015). Melatonin: Physiological effects in humans. *Neurochirurgie*, 61:77–84.
- [122] Tobeiha M, Jafari A, Fadaei S, Mirazimi SMA, Dashti F, Amiri A, et al. (2022). Evidence for the Benefits of Melatonin in Cardiovascular Disease. *Front Cardiovasc Med*, 9:888319.
- [123] Bano M, Chiaromanni F, Corrias M, Turco M, De Rui M, Amodio P, et al. (2014). The influence of environmental factors on sleep quality in hospitalized medical patients. *Front Neurol*, 5:267.
- [124] Mangini C, Zarantonello L, Formentin C, Giusti G, Domenie ED, Ruggerini D, et al. (2024). Managing Circadian Disruption due to Hospitalization: A Pilot Randomized Controlled Trial of the CircadianCare Inpatient Management System. *J Biol Rhythms*, 39:183–99.

- [125] Mastrullo V, van der Veen DR, Gupta P, Matos RS, Johnston JD, McVey JH, et al. (2022). Pericytes' Circadian Clock Affects Endothelial Cells' Synchronization and Angiogenesis in a 3D Tissue Engineered Scaffold. *Front Pharmacol*, 13:867070.
- [126] Abplanalp WT, John D, Cremer S, Assmus B, Dorsheimer L, Hoffmann J, et al. (2021). Single-cell RNA-sequencing reveals profound changes in circulating immune cells in patients with heart failure. *Cardiovasc Res*, 117:484–94.
- [127] Jamshed H, Steger FL, Bryan DR, Richman JS, Warriner AH, Hanick CJ, et al. (2022). Effectiveness of Early Time-Restricted Eating for Weight Loss, Fat Loss, and Cardiometabolic Health in Adults With Obesity: A Randomized Clinical Trial. *JAMA Intern Med*, 182:953–62.
- [128] Mure LS, Le HD, Benegiamo G, Chang MW, Rios L, Jillani N, et al. (2018). Diurnal transcriptome atlas of a primate across major neural and peripheral tissues. *Science*, 359:eaao0318.
- [129] Wen S, Ma D, Zhao M, Xie L, Wu Q, Gou L, et al. (2020). Spatiotemporal single-cell analysis of gene expression in the mouse suprachiasmatic nucleus. *Nat Neurosci*, 23:456–67.
- [130] Schrader LA, Ronnekleiv-Kelly SM, Hogenesch JB, Bradfield CA, Malecki KM. (2024). Circadian disruption, clock genes, and metabolic health. *J Clin Invest*, 134(14):e170998.
- [131] Dierickx P, Emmett MJ, Jiang C, Uehara K, Liu M, Adlanmerini M, et al. (2019). SR9009 has REV-ERB-independent effects on cell proliferation and metabolism. *Proc Natl Acad Sci U S A*, 116:12147–52.