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SLEEP AND HYPERTENSION (SJ THOMAS)

# Pressure Building Against the Clock: The Impact of Circadian Misalignment on Blood Pressure

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## Abstract

**Purpose of Review** Misalignment between the endogenous biological timing system and behavioral activities (i.e., sleep/wake, eating, activity) contributes to adverse cardiovascular health. In this review, we discuss the effects of recurring circadian misalignment on blood pressure regulation and the implications for hypertension development. Additionally, we highlight emerging therapeutic approaches designed to mitigate the negative cardiovascular consequences elicited by circadian disruption.

**Recent Findings** Circadian misalignment elicited by work schedules that require individuals to be awake during the biological night (i.e., shift work) alters 24-h blood pressure rhythms. Mechanistically, circadian misalignment appears to alter blood pressure via changes in autonomic nervous system balance, variations to sodium retention, dysregulation of endothelial vasodilatory responsiveness, and activation of proinflammatory mechanisms. Recurring circadian misalignment produced by a mismatch in sleep timing on free days vs. work days (i.e., social jetlag) appears to have no direct effects on prevailing blood pressure levels in healthy adults; though, circadian disruptions resulting from social jetlag may increase the risk of hypertension through enhanced sympathetic activation and/or obesity. Furthermore, social jetlag assessment may be a useful metric in shift work populations where the magnitude of circadian misalignment may be greater than in the general population.

**Summary** Circadian misalignment promotes unfavorable changes to 24-h blood pressure rhythms, most notably in shift working populations. While light therapy, melatonin supplementation, and the timing of drug administration may improve cardiovascular outcomes, interventions designed to target the effects of circadian misalignment on blood pressure regulation are warranted.

**Keywords** Circadian rhythms · Cardiovascular health · Blood pressure dipping · Shift work · Social jetlag

## Introduction

Cardiovascular disease is the leading cause of morbidity and premature mortality worldwide, with hypertension being the most prevalent modifiable risk factor [1]. While estimates predict that approximately 1.5 billion people will develop hypertension by 2025, blood pressure control remains poor globally [2]. A clear understanding of both endogenous and exogenous influences on blood pressure is thus needed in order to combat hypertension incidence. Blood pressure exhibits an endogenous near 24-h circadian rhythmicity and diurnal blood pressure rhythms are characterized by pressure surges in the morning during typical waketime, stable pressures across daytime/waking hours until an early evening peak, and then pressure falls or dips below waking values during typical sleep timing [3–6]. Moreover, attenuations in the blood pressure dipping magnitude during typical sleep timing appears to have implications for future cardiovascular risk. Specifically, individuals who do not decrease their overnight blood pressure by ≥ 10% from daytime blood pressure levels (i.e., "non-dippers") display stronger associations with increased risk of adverse cardiovascular events and mortality than those with only high office blood pressure measurements [7••]. Changes in overnight blood pressure dipping patterns may be driven by differences in circadian timing [8, 9•]; thus, not only is identifying factors that

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negatively impact the circadian rhythm of blood pressure critical for cardiovascular health, but also developing and implementing strategies to mitigate circadian disturbances may be a target for improved blood pressure outcomes.

The daily rhythms in physiological processes and behaviors have evolved over time to anticipate environmental changes occurring within the 24-h light/dark cycles. These circadian (derived from Latin with "circa" meaning approximate and "dian" meaning a day) rhythms are generated from the suprachiasmatic nucleus (SCN) within the hypothalamus (i.e., the central circadian clock) which then communicates to peripheral circadian oscillators throughout the body. As such, the timing of autonomic neural and hormonal outputs governed by the SCN enables appropriate blood pressure responses throughout the circadian cycle [10, 11]. This endogenous circadian blood pressure rhythm is robust in humans [3]; however, anatomical alterations to the SCN have been observed in hypertensive patients [12] suggesting a link between the circadian clock and disease. Recurring circadian disruptions or desynchronization of the circadian system may be one mechanism promoting adverse cardiovascular function.

The misalignment of behaviors with the internal biological timing system, such as with rotating and/or overnight shift work, is one such mechanism that may deteriorate cardiovascular health over time [13••]. Shift workers compose ~ 20% of the US workforce [14] and have up to a 40% increased risk of CVD and increased risk of hypertension development [15, 16, 17••, 18]. Shift work, however, is only one drastic form of circadian misalignment. Almost every individual worldwide experiences some form of circadian misalignment or disruptions in their lifetime, from time zone travel to early school start times to differences in sleep/wake times between work days and work free days (i.e., social jet lag); therefore, understanding how acute but potentially recurring circadian disruptions impact blood pressure has important health implications as well. While the circadian effects on hypertension and cardiovascular disease have been excellently examined by others [19••, 20, 21], this review will highlight recent findings relevant to the effects of circadian misalignment on blood pressure regulation, the evolving potential implications for hypertension development, and emerging therapeutic strategies designed to mitigate negative cardiovascular outcomes.

## Shift Work, Circadian Misalignment, and Blood Pressure

Shift work is a common cause of circadian disruption, as being awake and working outside of traditional daytime hours elicits changes to light exposure and behavioral activities such as sleep/wake, rest/activity, and fasting/eating [22]. Evidence suggests that a low percentage of permanent night workers experience partial or complete circadian entrainment (or synchronization of the biological clock with a new light/dark cycle) to nightshift work [23]; hence, a majority of shift workers experience recurrent rapid circadian rhythm desynchronization when shifting their sleep/wake cycles to being awake and working at night and sleeping during the day, then reverting back to a diurnal schedule on non-work days [23, 24]. This circadian rhythm desynchronization is similar to what is experienced when traveling rapidly across time zones. Entrainment to new external environmental cues (i.e., zeitgebers) occurs slowly [25], and greater shifts in timing correspond to a greater magnitude/duration of circadian misalignment. Moreover, exposure to zeitgebers promoting a day-time schedule (i.e., light exposure in the morning) interferes with or prevents circadian entrainment to a shift work schedule. The resulting circadian misalignment also increases the prevalence of impaired sleep quality and decreased sleep duration when individuals attempt to initiate sleep during the biological day [26–28]. As shown in Fig. 1, the circadian rhythm of melatonin (the gold-standard marker of circadian phase) is characterized by low levels during the circadian day, a sharp rise in the evening (i.e., dim-light melatonin onset [DLMO]), followed by a peak in the middle of the circadian night [29]. Amongst shift workers, however, behaviors become misaligned with circadian phase and sleep is typically initiated to occur during a time of low melatonin production [30]. Thus, daytime sleep initiation competes with the circadian promotion of alertness and thereby inhibits sleep onset and impairs consolidated sleep [31]. Consequently, individuals often revert back to sleeping during the circadian night on work-free days to recover from the insufficient sleep that accumulates during shift-working days [24, 28]. These recurring bouts of circadian misalignment elicited from abrupt circadian phase shifts is thought to be one underlying mechanism promoting poor health outcomes amongst shift workers [18, 22, 32, 33].

### Shift Work and 24-h Blood Pressure Rhythms

The prevalence of hypertension in shift workers is equivocal, with evidence indicating either a 12–18% increase in hypertension incidence or no association between high blood pressure and shift work [33–37]; though age, years of shift work, and sleep duration may play a role in disease pathophysiology [38–40]. However, across various professions that include some form of shift work schedule, applied research has shown alterations to blood pressure regulation and rhythmicity elicited by circadian misalignment [9•, 41, 42•, 43–47], which may have greater implications for overall cardiovascular health rather than hypertension development, per se. Chau and colleagues were the first to report that shift workers not only had higher systolic and diastolic

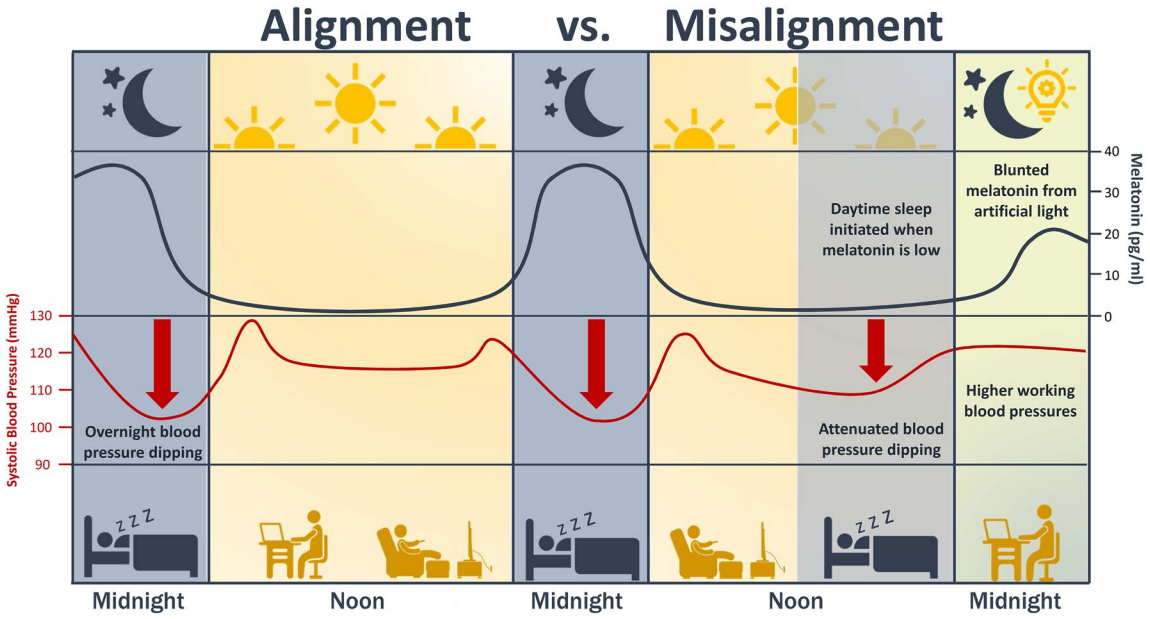


**Fig. 1** Blood pressure rhythms with circadian alignment vs. circadian misalignment (*left to right*). When behaviors are aligned with the internal biological timing system (illustrated by the melatonin rhythm), diurnal blood pressure fluctuations are characterized by morning pressure surges, stable pressures across daytime/waking hours, a second evening peak, followed by overnight blood pressure dipping during sleep (≥ 10% from daytime values). Circadian misalignment, such as that experienced with shift work, results in attenuated blood pressure dipping during daytime sleep episodes, higher pressures during working hours, and blunted melatonin rhythms resulting from artificial light exposure

pressures during their circadian-misaligned work shifts, but also exhibited higher pressures for a longer duration across a 24-h circadian cycle compared to day shift workers [48]. This has also been reported by others [41, 43, 49, 50•], though not supported by all [51, 52]. However, augmented working blood pressure and a blunted circadian rhythm of blood pressure has been observed within rotating shift workers when individuals worked the circadian misaligned night shifts as compared to the circadian aligned day-work schedule [44, 46]. These data provide compelling evidence that shift work combined with circadian misalignment uniquely affects blood pressure control, though the independent effect of circadian misalignment cannot be interpreted from these field study designs.

Laboratory experiments have been developed to precisely identify the circadian influence on various biological processes. By using controlled in-laboratory techniques, such as a rapid inversion of sleep/wake timing (i.e., a "slam-shift" protocol) or equally spreading behaviors across the 24-h day by utilizing daylengths that differ from the 24-h day (i.e., a "forced desynchrony" protocol), the underlying mechanisms that govern blood pressure responses to circadian alignment vs. misalignment can be investigated to better understand how circadian disruption contributes to cardiovascular risk. Short term, in-laboratory circadian misalignment protocols have been shown to elicit acute increases in arterial pressures and inflammatory markers in healthy, non-shift working adults [8, 53]. To expand upon these findings, Morris and colleagues sought to determine if similar effects occurred in chronic nightshift workers [54]. Participants underwent two 3-day laboratory protocols: a circadian aligned visit and a simulated nightshift schedule visit whereby a rapid 12-h shift in behavioral activity was implemented. Circadian misalignment elicited a modest yet meaningful increase in 24-h systolic (+ 1.4 mmHg) and diastolic (+ 0.8 mmHg) blood pressure, which was mediated by elevated systolic pressure during wakefulness (+ 1.7 mmHg) and increased diastolic pressure during sleep (+ 1.8 mmHg). Additionally, 24-h levels of C-reactive protein, a marker of systemic inflammation, were significantly elevated with misalignment [54]. Moreover, evidence suggests that circadian misalignment, particularly when accompanied by sleep restriction, may further promote the dysregulation of arterial pressures via changes in autonomic nervous system balance [4, 8, 55–57] and/or sodium retention [58•]. Investigations directly measuring basal muscle sympathetic nerve activity amongst shift workers, however, is lacking. Taken together, these findings highlight the cardiovascular consequences of shift work induced circadian misalignment.

## Shift Work and Blood Pressure Dipping

Impaired blood pressure recovery following a night shift [44, 46] and increased prevalence of non-dipping overnight blood pressure patterns [43, 44, 46–48, 50•, 59, 60], particularly amongst African Americans [45], further contributes to the diminished circadian blood pressure rhythm observed in shift workers (Fig. 1). Importantly, McHill and colleagues demonstrated that changes to overnight blood pressure dipping occurs rapidly (within 90 days) when transitioning into a shift working schedule [42•] and this attenuated overnight blood pressure dipping profile persists amongst chronic shift workers (average of 9 years of working a shift work schedule) [9•]. In shift workers with hypertension, the diurnal blood pressure rhythm changes from a dipper to a non-dipper pattern within the first day of nightshift work, though the rhythm returns to a dipping pattern after a few days of nightshift work [43]. Taken together, these findings suggest that alterations to the overnight blood pressure dipping pattern changes rapidly and that individuals with existing comorbidities may be more acutely vulnerable to the adverse cardiovascular effects of shift work.

While mechanisms driving overnight blood pressure dipping remain poorly understood, evidence suggests that the degree of overnight blood pressure dipping better predicts adverse cardiovascular events independent of average daytime blood pressure levels [61–63]. Adverse overnight blood pressure dipping profiles accompanying the transition into shift work has been shown to be associated with increased sleep onset timing variability [9•, 42•], potentially implicating the role of increased circadian disruption on vascular function. Sleep disturbances and reductions in total sleep time appear to alter neurocirculatory mechanisms that likely underlie the changes to overnight blood pressure dipping observed. Generally, integrative mechanisms balance autonomic nervous system output with vascular endothelium derived vasodilatory factors to maintain vascular tone [64]. However, evidence suggests that sleep restriction (i.e., < 6 h per night) combined with circadian misalignment disrupts overall sympathovagal balance, whereby parasympathetic tone is diminished and sympathetic nervous system influence appears enhanced [55, 65]. Additionally, arousals during sleep are associated with transient changes in autonomic outflow, resulting in brief blood pressure surges [66]. Thus, sympathetically mediated peripheral vasoconstriction and transient increases in blood pressure could constrain blood pressure dipping magnitude further. Finally, functional impairments of the vascular endothelium elicited by sleep restriction and circadian misalignment may promote increased peripheral resistance via attenuated vasodilatory capacity and activation of proinflammatory mechanisms [8, 53, 54, 67, 68]. In summary, augmented sympathetic activity, blunted parasympathetic tone, and early indicators of compromised cardiovascular function may pathologically drive higher arterial pressures during daytime sleep in shift workers and increase the risk of cardiovascular disease.

## Social Jetlag and Blood Pressure

In humans, the average circadian period is slightly longer than the 24-h day [69]; therefore, most individuals must entrain their biological clocks daily. Entrainment characteristics are influenced by genetics, age, sex, and environmental factors like light exposure, creating a range of individual diurnal preferences or chronotype [70]. The three primary chronotypes are morning-, neither-, or evening-types, with roughly 40% of the adult population being classified as either a "morning" or "evening" person [71]. In general, males are more likely to be evenings types, though a shift towards a morningness preferences is associated with age regardless of sex [72, 73]. In recent decades, there has been a growing interest in assessing the potential health outcomes associated with chronotype and recurring small circadian disruptions leading to a phenomenon known as social jetlag. The term social jetlag refers to discrepancy between the sleep timing imposed by the social clock (i.e., work/school schedules) and the biologically driven sleep timing occurring on work-free days, causing an effect akin to flying rapidly across time zones (i.e., jetlag). It is proposed that evening chronotypes experience greater social jetlag as they have a preference to sleep and wake later on work-free days but have to adjust to early hours on working/school days [74]. As such, social jetlag could be viewed as an acute but chronically occurring form of circadian misalignment.

There is limited information regarding global prevalence rates of social jetlag, though estimates range from 30 to 70% of individuals experiencing at least 1 h of social jetlag per week [74–77, 78•] and roughly one third of individuals experiences ≥ 2 h of social jetlag in the general adult population [74, 77]. Some evidence suggests that social jetlag is associated with adverse cardiometabolic risk factors such as abnormal lipid profile, insulin resistance, increased waist circumference, adiposity, and body mass index [74, 79–81]; though this is not a universal finding [77, 78•] and social jetlag may only be related to increased body mass index amongst already overweight/obese individuals [74]. However, few studies have examined how social jetlag impacts blood pressure and risk of hypertension development.

To date, there have been no reported effects of social jetlag on systolic or diastolic blood pressure in adults younger than 30 years [77, 78•]. Rutters and colleagues were the first to examine the role of social jetlag on endocrine and cardiovascular risk profiles in a healthy population [77]. Participants were classified as experiencing either ≤ 1 h ($n = 55$), > 1 h and < 2 h ($n = 53$), or ≥ 2-h social jetlag

($n = 37$). While there were no differences in blood pressure measures between social jetlag groups, social jetlag was associated with elevated heart rates and cortisol levels (a hormone mediating the body's stress response), suggesting a shift towards greater sympathetic influence [77]. McMahon and colleagues also reported no effect of social jetlag on cardiovascular outcomes in a young (21–35 years), ostensibly healthy population of males and females [78•]. Rather, sleep disruptions amongst morning types were associated with increased odds of obesity and elevated blood pressures [78•]. Finally, in healthy but overweight midlife adults (average age 43 years; body mass index 27 kg/m$^2$), neither chronotype nor social jetlag was shown to be correlated with resting heart rate or blood pressure [79]. Taken together, these findings would suggest that circadian disturbances play a more profound role on obesity and ultimately obesity-related increases in arterial pressure, rather than direct effects of social jetlag on blood pressure, per se [82]. Nonetheless, the effects of circadian misalignment elicited by social jetlag on hypertension-promoting mechanisms, such as changes in autonomic balance and endothelial function, remain to be investigated. Furthermore, the extent to which these mechanisms may vary by sex warrants further exploration. Indeed, evidence suggests that males and females maintain normal arterial pressures through different physiological pathways [83–87]. Female sex hormones have been implicated in β-adrenergic receptor mediated vasodilation with sympathetic activation, rather than the typical α-adrenergic receptor mediated vasoconstrictive response [87]. If circadian disruptions resulting from social jetlag and/or chronotype do, in fact, elicit an increase in systemic sympathetic activation, increases in peripheral resistance and blood pressure would likely be offset by these protective mechanisms, at least in pre-menopausal females. However, the combined effects of a greater reliance on autonomic support of blood pressure with age and the loss of sex hormones post-menopause [87, 88] may exacerbate the autonomic and vascular effects of circadian disturbances in females later in life, when the risk of hypertension is increased.

Amongst shift workers experiencing a greater degree of social jetlag (≥ 4 h), high prevalence rates of hypertension (25%) have been reported; though, it is unclear to what extent confounding factors such as smoking (~ 79% prevalence) contribute to disease pathophysiology in this population [89•]. Recent work from Vieira and colleagues examined the relationship between social jetlag and melatonin production amongst shift workers [90]. While blood pressure outcomes were not assessed, findings from this investigation may provide insight into mechanisms underlying disturbed cardiovascular regulation. Authors report that, expectedly, nightshift workers had lower sleep durations compared to dayshift workers. However, nightshift workers experienced a 13-fold higher degree of social jetlag (Δ9.8 h), which was associated with greater inhibition of nocturnal melatonin production [90]. Indeed, evidence suggests that melatonin rhythms are disrupted by nightshift work [30], likely contributing to overall social jetlag severity and potentially promoting adverse blood pressure consequences via impaired antioxidant and anti-inflammatory effects of melatonin [91, 92]. While more research is needed, social jetlag could be a useful metric when considering the magnitude of circadian misalignment, particularly in shift working populations where individuals may be at higher risk for negative cardiovascular health outcomes.

## Circadian Clock Mechanisms and Blood Pressure

Circadian rhythms are driven by molecular circadian clocks located in nearly every tissue and organ in the body that oscillate autonomously across a ~ 24-h period, even when external environmental cues (i.e., zeitgeber) are absent [69]. The central circadian clock located in the SCN is entrained by light and is the internal pacemaker synchronizing peripheral clock mechanisms to align downstream clock-dependent gene expression with the daily light/dark cycle. These molecular clock mechanisms consist of a series of transcription-translation feedback loops that drive circadian variation in tissue specific gene synthesis that ultimately facilitate physiological processes, including blood pressure regulation [19••]. Indeed, circadian misalignment in healthy men has been shown to upregulate proteins and signaling pathways that promote poor cardiovascular outcomes [93]. The circadian rhythm of blood pressure is likely governed by numerous integrative mechanisms including but not limited to diurnal changes in circulating levels of catecholamines, baroreflex sensitivity, autonomic balance, sodium retention, endothelial function, and sympathetically-mediated α-adrenergic receptor responsiveness [4, 6, 58•, 94–96], with evidence from animal models directly implicating the role of clock proteins in the normal functioning of these processes [97–99].

Clock mechanisms not only affect targeted gene expression, but emerging evidence also implicates the role of specific clock genes in prevailing blood pressure in humans. Briefly, the core clock proteins consist of two activator proteins BMAL1 (brain and muscle aryl-hydrocarbon receptor) and CLOCK (circadian locomotor output cycles kaput) and two repressor proteins PER (period) and CRY (cryptochrome) [19••]. Toffoli and colleagues recently reported that rotating shift work is associated with increased arterial pressures and heart rate values during working hours and reduced blood pressure dipping during sleep, similar to what has been reported previously [50•]. However, nightshift work elicited a significant upregulation in the expression of most clock genes, with

an independent association between nightshift blood pressure and PER2-3 gene expression being observed [50•]. Indeed, outside of core molecular clock mechanisms, evidence suggests that PER plays a critical role in blood pressure regulation and sodium handling [100, 101], though other clock genes have been implicated [19••]. Yet, light exposure stimulates a rapid increase in *Per* mRNA expression within the SCN and clock gene rhythm resetting [102]; thus, PER may provide a distinct mechanistic link between light-induced circadian misalignment and poor blood pressure outcomes, particularly amongst shift workers. Proposed mechanisms contributing to elevated blood pressures elicited by circadian disturbances are illustrated in Fig. 2.

## Therapeutic Approaches to Mitigate Circadian Misalignment

There are significant health implications for developing strategies that prevent or alleviate the negative cardiovascular consequences associated with shift work-induced circadian misalignment. While not all shift workers develop hypertension, abundant evidence shows a distinct impairment to circadian blood pressure rhythms which in turn promotes cardiovascular disease risk. Indeed, epidemiological evidence shows that improvements in blood pressure, particularly systolic blood pressure, reduce the risk of cardiovascular disease and mortality even amongst individuals not meeting the threshold for clinical hypertension (i.e., ≥ 140/90 mmHg) [103, 104]. Complete circadian adaptation to shift work has been observed under some circumstances, particularly amongst offshore petroleum workers where 24-h operations are more standardized [105]; however, adequate circadian entrainment is not observed in a large percentage of shift workers [23]. Numerous interventions have been employed to improve individual adaptations to shift work, though the applicability of "real world" implementation is unclear. Furthermore, evidence supporting the effectiveness of such circadian interventions on cardiovascular outcome measures is limited.

Seminal studies have shown a greater tolerance to shift work and improved health when working schedules are adjusted to promote gradual circadian phase delays [106], with modest improvements to systolic blood pressure [107], yet additional research is needed to support these findings. Supplemental melatonin appears to show some effectiveness in improving daytime

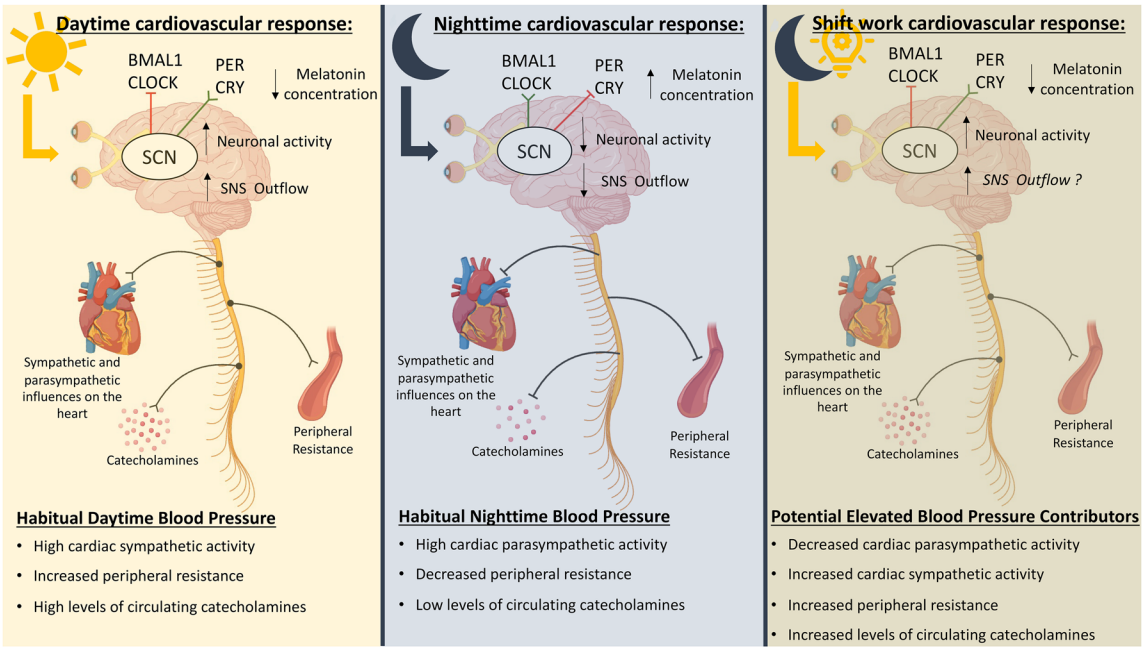


**Fig. 2** Cardiovascular responses to daytime, nighttime, and shift work. Blood pressure rhythms are affected by light, which directly increases neuronal activity in the suprachiasmatic nucleus (SCN). Environmental stimuli are communicated to autonomic nervous centers in the brain to alter autonomic outflow and trigger changes to circulating levels of catecholamines which contribute to increased peripheral vascular resistance and greater blood pressure during the day (*left panel*) and decreased peripheral vascular resistance and lower blood pressures at night (*middle panel*). Though not as bright as solar light, artificial light exposure at night can influence these regulatory pathways (*right panel*). With shift work, blood pressure elevations appear to be mediated by decreased cardiac vagal tone, increased sympathetic activity, and increased circulating catecholamines. Other potential mechanisms include increases in muscle sympathetic nerve activity and changes in α-adrenergic receptor sensitivity promoting enhanced vasoconstriction and peripheral resistance; diurnal and/or circadian rhythms in baroreflex sensitivity; altered endothelial function resulting from upregulated inflammatory pathways; and changes in sodium handling. Created with icons from BioRender.com

sleep episodes [108], which may directly or indirectly improve overnight blood pressure dipping patterns. Indeed, in healthy men, 1 mg of melatonin improved waking blood pressure measures via decreased pulsatility index and norepinephrine levels [109]. In men with essential hypertension, 3 weeks of melatonin use improved daily blood pressure rhythms and increased blood pressure dipping magnitude [110]. While investigations in a shift working population are warranted, these data collectively suggest that melatonin could be a beneficial treatment strategy for mitigating the effects of circadian misalignment while concurrently favorably supporting blood pressure. The use of light therapy to promote circadian shifts appears to yield promising results. Circadian entrainment to nightshift work has improved when individuals were exposed to bright light during their night shift and use dark goggles to shield from morning light on the commute home [111–113], with some discrepant findings from others [114••]. Despite light therapy showing no effect on melatonin rhythms in rotating shift workers, Hannemann and colleagues showed significant effects of light intervention on overnight blood pressure dipping [114••]. Not only did light therapy elicit a ~ 9 mmHg reduction in sleep blood pressure, but also the magnitude of blood pressure dipping persisted up to 12 weeks post-intervention [114••]. Thus, appropriately timed light exposure might have the most robust effects on blood pressure outcomes in shift workers.

Finally, a growing interest in chronotherapeutic strategies has begun to examine the effectiveness of drug timing on both basal blood pressure levels, circadian driven blood pressure rhythms, and cardiovascular endpoints. With overnight blood pressure dipping appearing to better predict adverse health outcomes compared to daytime pressures, evening dosing of antihypertensive medications may provide more cardioprotective effects by improving nighttime blood pressures while attenuating the morning pressure surge. The safety and efficacy of chronotherapy for hypertension management has been excellently reviewed by others [115, 116, 117••], highlighting that improved 24-h blood pressure profiles and cardiovascular endpoints have been reported with evening use of blood pressure lowering medications in daytime workers in several clinical trials. However, improved outcomes from bedtime medication use is not a unanimous finding [118] and differences between study design, such as the concomitant use of morning medication, underscores the need for more clarity in this area [119–121]. Observational data from 1546 patients and 24-h administration of medications (~ 500,000 doses), including but not limited to antihypertensives, has shown greatest clinical responsiveness when drugs were given at night [122••]. Furthermore, recent findings from the HYGIA Chronotherapy trial report significant decreases in cardiovascular events, improved sleep-time blood pressure, and improved blood pressure dipping patterns despite modest improvements to 48-h systolic blood pressure measures (− 1.3 mmHg) with bedtime medication use [123]. Of note, these robust outcomes are contrary to findings from other clinical trials and caution is warranted when interpreting these results [124]. Future results from the currently ongoing prospective, multicenter clinical trials Treatment In Morning versus Evening (TIME) and Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed) should provide more insight [125, 126]. Considering a majority of top-selling medications, including classes of blood pressure medications, target genes that are circadian-controlled [127], more research is needed to clarify the effect of chronotherapy on blood pressure and what benefits, if any, it may have on cardiovascular risk profiles in individuals where recurring circadian misalignment is a feature.

## Conclusions

Misaligning behaviors with the endogenous circadian system results in adverse alterations to 24-h blood pressure rhythms, most notably in shift working populations. Numerous blood pressure regulatory mechanisms appear to be disrupted with circadian misalignment, such as altered autonomic balance, upregulated inflammatory pathways, and changes in sodium retention. Bright light therapy shows promising effects on blood pressure outcomes in shift workers, though more research is needed. Despite conflicting evidence of hypertension prevalence in presumably circadian-misaligned shift working populations, improved blood pressure control has significant implications for overall health and reduction of cardiovascular disease risk. While acute, recurring circadian disruptions elicited by social jetlag do not appear to have clear impacts on average prevailing blood pressures in healthy adult populations, evidence suggests that social jet lag may impact blood pressure regulation either through the development of obesity or other hypertension-promoting pathways, such as autonomic nervous system imbalance. Furthermore, social jetlag may be a useful metric in assessing the magnitude of circadian disruption in populations vulnerable to circadian misalignment (i.e., shift workers). There are significant public health implications for individuals experiencing higher degrees of circadian misalignment and more research is needed to develop therapeutic strategies designed to promote better circadian adjustments.

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**Data Availability** Published data will be made available upon request to any qualified researcher via email to the corresponding author.

## Compliance with Ethical Standards

**Conflict of Interest** Andrew McHill, PhD, consults for Pure Somni Corporation. The remaining authors have no conflicts of interest to declare.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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