

Review

Sleep disorders, nocturnal blood pressure, and cardiovascular risk: A translational perspective

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ABSTRACT

Cardiovascular disease (CVD) represents the first cause of death globally. The nighttime is generally a period of relative protection from CVD events such as myocardial infarction, sudden cardiac death, and stroke, at least compared to the early morning period. The nighttime also generally entails lower values of arterial blood pressure (ABP) and heart rate (HR) and higher cardiac parasympathetic modulation. These day-night cardiovascular rhythms are ultimately driven by circadian molecular oscillators in the hypothalamic suprachiasmatic nucleus and in peripheral cells, including those in the heart, blood vessels, and kidneys. The wake-sleep states are intermediate mechanisms of circadian cardiovascular regulation, with non-REM sleep decreasing ABP and HR and increasing cardiac parasympathetic modulation at the beginning of the night. Obstructive sleep apnea, insomnia, and the restless legs syndrome have high prevalence in the general population and may increase nighttime cardiovascular activity and CVD risk. CVD risk is better predicted by ABP values during nighttime sleep than during daytime wakefulness. Higher nighttime values of ABP and HR increase cardiac work and vessel wall stress. During the night, circadian rhythms may enhance cardiac responses to hypertrophic stimuli, increase vascular smooth muscle Rho kinase activity and contractility, decrease endothelial nitric oxide production and vascular responses to vasodilators, and increase circulating monocytes with the potential to infiltrate atherosclerotic plaques. Together, these factors configure a “perfect storm” scenario that may make increased cardiovascular activity during the night a final common mechanism linking sleep disorders to CVD risk.

1. Introduction

The interest for the cardiovascular (CV) implications of sleep-related topics has been steadily increasing for the past 20 years, as revealed by increasing paper publication rates either in absolute terms or relative to other publications in the sleep field. However, the physiology, pathophysiology, and clinical implications of the links between sleep and CV control remain contentious topics. At least in part, this may be because of the intrinsic complexity of a highly interdisciplinary field, which encompasses clinical research on different sleep disorders and CV disease (CVD), chronobiology, and cardiology, as well as mechanistic pre-clinical research on animal models. This review aims to provide a broad narrative overview of these different facets of research on the CV implications of sleep disorders.

2. Epidemiology, pathophysiology, and chronobiology of CVD events

2.1. CVD is the main cause of death at the global level

The World Health Organization (WHO) estimated that almost 18 million people died from CVD in 2016. CVD represented the first cause of death globally, accounting for 31% of all deaths. Of these deaths, 85% were due to coronary heart disease and cerebrovascular disease, including myocardial infarction, sudden cardiac death, and stroke (WHO, 2017). Hypertension is among the most important intermediate risk factors for death due to CVD (WHO, 2017), with an age-standardized prevalence ranging from 18% to 30% in the European Union (Timmis et al., 2018).

2.2. CVD events are associated with atherosclerosis plaque burden

The key pathophysiologic process underlying sudden cardiac death, myocardial infarction, and stroke due to thrombosis is thought to be

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rupture of vulnerable atherosclerotic plaques, triggered by hemodynamic stress, and progressing to complete vessel occlusion particularly in conditions of vasoconstriction and increased coagulability (Muller, 1999). The typical rupture-prone vulnerable plaques are fibroatheromas with a large necrotic core and a thin cap infiltrated by macrophages, which degrade collagen and elastin by releasing proteases (Bentzon et al., 2014). Vulnerable plaques may convert to a non-vulnerable phenotype with an apparently stochastic process (Stefanadis et al., 2017). Therefore, the overall atherosclerotic disease burden, a measure of the extent of atherosclerosis irrespective of cellular composition and activity of plaques, determines CVD risk better than the occurrence of any single vulnerable plaque (Arbab-Zadeh and Fuster, 2015). Because atherosclerosis is a multifocal disease affecting the entire vasculature, markers of atherosclerosis burden in a vascular territory, such as the carotid intima-media thickness, may also signal burden in other territories, such as the coronary circulation (Bentzon et al., 2014).

2.3. The occurrence of CVD events shows a marked day-night rhythm

CVD events resulting from coronary heart disease and cerebrovascular disease, including myocardial infarction, sudden cardiac death, and stroke, have a distinct day-night pattern of occurrence, with a marked peak in the morning hours (Marler et al., 1989; Mulcahy et al., 1988; Muller et al., 1989; Reavey et al., 2013; Willich et al., 1987). Sudden cardiac death also shows a clear-cut decrease in incidence during the first part of the night (Willich et al., 1987). The morning peak in incidence explains approximately 1 of 11 acute myocardial infarctions and 1 of 15 sudden cardiac deaths (Cohen et al., 1997), and entails a 79% increase in stroke risk over the remaining 18 h of the day (Elliott, 1998). Careful analyses reasonably ruled out the hypotheses that the morning peak in incidence of CVD events is an artifact due to CVD events that occur during sleep and that remain either subjectively unrecognized or objectively unwitnessed until the following morning (Muller, 1999). Taken together, these results demonstrate that the nighttime does not entail increased risk of CVD events and may actually confer protection from these events, particularly in comparison with the morning period.

2.4. Autonomic and hemodynamic rhythms parallel the day-night rhythm of CVD events

In the vast majority of subjects, ABP and HR are higher during the daytime than during the nighttime. The day-night differences in ABP and HR average approximately 15 mmHg and 15 beats per minute, respectively, but with wide variability between subjects (Staessen et al., 1997) and within subjects (Cuspidi et al., 2007). The fall in ABP from daytime to nighttime is generally normalized by expressing it as a percentage of the daytime ABP value. This yields the so-called ABP “dip”, which is considered normal if between 10% and 20% (Hermida et al., 2013). A similar “dip” can be computed for the values of HR (Cuspidi et al., 2018). The daytime also entails greater variability of ABP and HR and a sharp decrease in the parasympathetic modulation of HR compared to the nighttime (Van de Borne et al., 1994). Cardiac parasympathetic control protects against potentially lethal ventricular arrhythmias that lead to sudden cardiac death (Billman, 2006; Ng, 2014). On the other hand, the morning hours entail a “morning surge” of ABP compared to the preceding nighttime ABP values (Bilo et al., 2018; Fujiwara et al., 2017). The morning hours also entail wide fluctuations in blood viscosity (Ehrly and Jung, 1973), which may be caused by increases in hematocrit (Touitou et al., 1986) and concomitant decreases in blood fibrinolytic activity (Rosling et al., 1970). Thus, the daytime, and particularly its early morning hours, may provide conditions of hemodynamic stress leading to vulnerable plaque rupture, increased coagulability that promotes complete vessel occlusion, and increased myocardial work that aggravates the consequences

of any impairment in coronary flow.

3. Physiological mechanisms of day-night autonomic and hemodynamic rhythms

3.1. The autonomic CV control during the daytime depends on the wakefulness behavior

At least in hypertensive subjects, the extent of ABP variability during the daytime in real-life conditions correlates with the reactivity of ABP to physical exercise or mental stress tests in the laboratory (Floras et al., 1987). Increases in the occurrence rate of acute myocardial infarction, particularly in subjects with known coronary heart disease, were recorded in Germany within two hours from the start of World Cup soccer matches that involved the German team (Wilbert-Lampen et al., 2008). This result supports the potential for emotional stress during wakefulness to trigger CVD events, possibly by triggering vulnerable plaque rupture as a result of increased CV activity. The assumption of the sitting and, even more so, of the standing posture during wakefulness may also be relevant in this respect, as it entails increases in ABP and HR and a marked decrease in the parasympathetic modulation of HR (Silvani et al., 2017).

3.2. The autonomic CV control during the nighttime depends on the sleep behavior

The state of non-rapid-eye-movement (non-REM) sleep accounts for approximately 80% of sleep time in human subjects, and is prevalent at the beginning of the night (Carskadon and Dement, 2011). Non-REM sleep decreases the mean values and the variability of ABP and HR compared to wakefulness (Silvani et al., 2008). During REM sleep, which accounts for the remaining 20% of sleep time in human subjects and is prevalent at the end of the night (Carskadon and Dement, 2011), the values of these variables return towards their levels during wakefulness (Silvani et al., 2008).

The autonomic and hemodynamic mechanisms that underlie the effects of non-REM and REM sleep on ABP and HR are controversial (Silvani, 2008). Recent data indicate that at least in mice, the decrease in ABP during non-REM sleep compared to wakefulness is entirely due to a decrease in the adrenergic vasoconstrictor activity, whereas the increase in ABP from non-REM sleep to REM sleep is due to a combined increase in sympathetic activity to the heart and to blood vessels (Lo Martire et al., 2018). Accordingly, different lines of evidence on human subjects and animal models indicate that non-REM sleep decreases the sympathetic nerve activity (SNA) to skeletal muscles blood vessels, kidneys, and skin compared to wakefulness (Silvani, 2017; Silvani and Dampney, 2013). REM sleep increases SNA to skeletal muscle blood vessels (Somers et al., 1993), while it decreases, at the same time, SNA to the splanchnic and kidney beds (Silvani, 2008).

These basic research data fit with the recent finding that vascular resistance undergoes an overnight decrease in hypertensive subjects, which is the greater with greater decreases in ABP (Sherwood et al., 2018). However, other lines of evidence on human subjects (Veerman et al., 1995) and animal models (Kurtz et al., 2014; Talan and Engel, 1989) indicate that the nocturnal decrease in ABP is caused by a decrease in cardiac output, which is incompletely compensated by an increase in vascular resistance. This nightly decrease in cardiac output has been attributed to a decrease in blood volume, itself due to negative water balance because of cessation of drinking during sleep in the face of continuing water loss (Talan et al., 1992; Touitou et al., 1986). The mechanisms of the nocturnal increase in vascular resistance reported by these studies are also unclear, as this increase is either unaffected or even enhanced by blockade of adrenergic receptors (Talan and Engel, 1989). It is unclear whether cardiac output decreases during non-REM sleep compared to wakefulness in human subjects and animal models (Silvani, 2008). Nonetheless, non-REM sleep and REM sleep entail

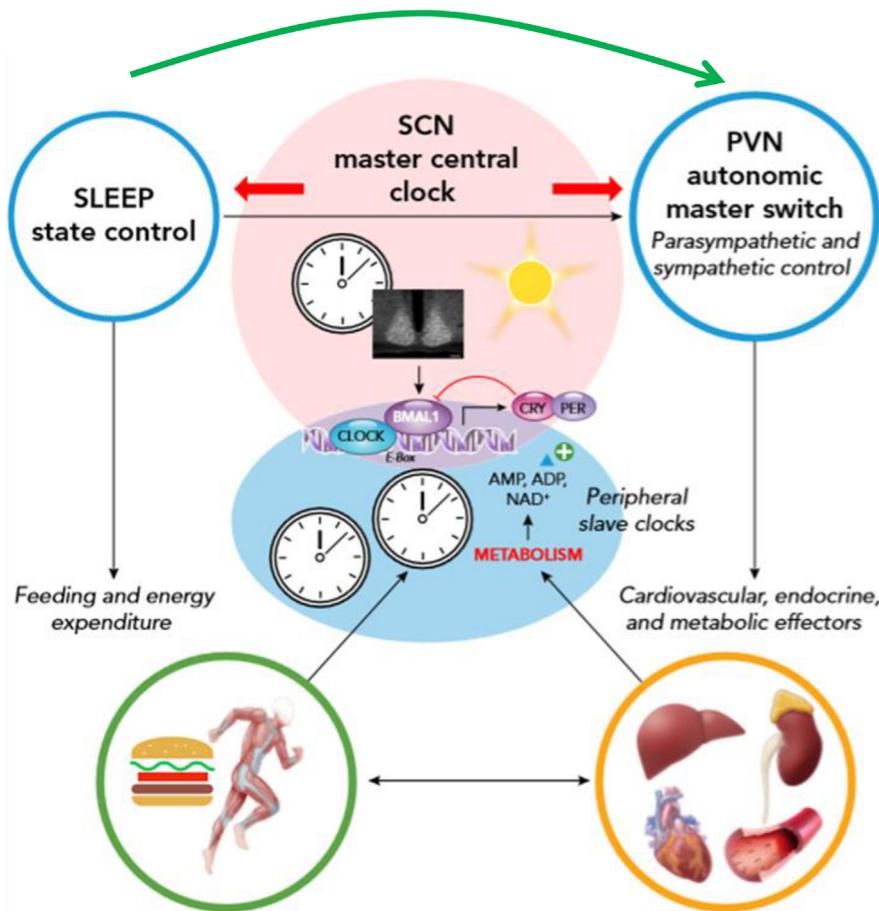


Fig. 1. Circadian and sleep-related control of cardiovascular, endocrine, and metabolic factors.

The master circadian clock in the neurons of the hypothalamic suprachiasmatic nucleus (SCN) exerts direct control on autonomic rhythms with neural pathways that involve the hypothalamic paraventricular nucleus (PVN). The SCN clock entrains molecular clocks in peripheral cells, including those of cardiovascular, endocrine, and metabolic effectors, which are sensitive to the cellular metabolic state. The SCN clock also drives circadian rhythms of wake-sleep states, which are an important intermediate mechanism of circadian cardiovascular control (green arrow). **CLOCK**, **BMAL1**, **CRY**, and **PER**, key proteins coded by homonymous core clock genes; **AMP** and **ADP**, adenosine mono- and diphosphate, respectively; **NAD+**, oxidized nicotinamide adenine dinucleotide. Modified from Silvani et al., 2018, with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

decreases and increases in HR, respectively (Silvani, 2008). In mice, these changes in HR result from a decrease in parasympathetic activity and an increase in sympathetic activity during non-REM sleep, the opposite occurring during REM sleep (Lo Martire et al., 2018). Non-REM sleep also entails an increase in the parasympathetic modulation of HR compared to wakefulness (Lo Martire et al., 2018; Van de Borne et al., 1994).

The CV activity during non-REM sleep is reduced on average compared to wakefulness, but it may be transiently increased as a result of short-lasting changes in brain and muscle activity including arousals (Silvani et al., 2015), limb movements (Ferri et al., 2017), and apneas (Somers et al., 1995). In particular, arousals from non-REM sleep entail increases in ABP and HR with magnitude similar to the average decrease in these variables during the nighttime compared to the daytime (Silvani et al., 2015). As a result, repeated arousals limit the decrease in ABP entailed by non-REM sleep (Carrington and Trinder, 2008). Leg movements during sleep also entail substantial increases in ABP and HR, particularly in association with microarousals (Pennestri et al., 2007).

The autonomic and hemodynamic mechanisms that underlie the CV changes associated with arousals and limb movements during sleep are still unclear. These mechanisms may include an increase in vascular resistance in the face of a decrease in stroke volume (Morgan et al., 1996), as a result of central autonomic commands that transiently override the baroreceptor reflex (Silvani et al., 2011). Obstructive sleep apnea (OSA) entails a progressive decrease in HR, which is followed by a sharp rise in HR and ABP upon resumption of breathing, often in association with an arousal. These CV changes result from a complex interplay between autonomic correlates of arousal, chemoreceptor and baroreceptor reflexes, autonomic effects of activation of chest and lung mechanosensitive afferents, and hemodynamic effects of the changes in

pleural pressure associated with the inspirations against obstructed upper airways (Somers et al., 1995). Central sleep apneas also entail transient CV changes, which are less studied but of potential clinical relevance (O'Driscoll et al., 2009).

3.3. Circadian rhythms drive the day-night distribution of wakefulness and sleep

The propensity to stay awake during the day and to spend most of the night asleep reflects the interaction between the amount of time previously spent in wakefulness or sleep (the so-called homeostatic control of sleep) with a strong circadian control (Daan et al., 1984). This interaction between homeostatic and circadian processes in the control of sleep has been formalized with an influential theoretical model, the 2-process model, without considering the sleep stages and their temporal pattern across the night. However, the proxy variable employed in the model to estimate the sleep homeostatic process in humans was the integrated power density of the electroencephalogram, which is the highest during the deeper stages of non-REM sleep, prevailing at the beginning of the night (Daan et al., 1984). Other studies have indicated that the increased REM sleep propensity at the end of the night and during the early morning is also due to interactions between circadian propensity and homeostatic drive (Wehr et al., 2001; Werth et al., 2002; Wurts and Edgar, 2000). Circadian rhythms thus play an important role in determining not only the distribution of sleep and wakefulness between the rest and activity periods, but also of non-REM sleep and REM sleep during the rest period.

Circadian rhythms are endowed with an endogenous “free-running” period of approximately 24 h (Roenneberg and Merrow, 2016). This property results from cell-autonomous interconnected sets of delayed negative-feedback circuits sensitive to the cellular energy status, which

involve processes of gene transcription and translation and protein transport and degradation (Eckel-Mahan and Sassone-Corsi, 2013).

The master circadian oscillator is a collective property of neurons in the hypothalamic suprachiasmatic nuclei (SCN). The SCN oscillator is responsible for the circadian rhythms of sleep and wakefulness (Fig. 1) through multi-synaptic connections with other hypothalamic structures, such as the lateral hypothalamic area and the ventrolateral pre-optic nucleus (Saper et al., 2005).

3.4. The wake-sleep behavior is an intermediate mechanism of the circadian autonomic control of the CV system

Projections from the SCN to the hypothalamic paraventricular nucleus (PVN) control separate populations of pre-sympathetic and pre-parasympathetic neurons (Buijs et al., 2003), and may play an important role in circadian rhythms of autonomic CV control (Fig. 1). There is robust evidence of circadian rhythms of ABP and HR in human subjects under unmasking conditions, which control for changes in wakefulness-sleep behavior and light-dark cycles (Krauchi and Wirz-Justice, 1994; Shea et al., 2011). In these unmasking conditions, the peak and trough of the circadian rhythm of HR occur at the beginning of the subjective activity period and at the end of the subjective rest period, respectively (Krauchi and Wirz-Justice, 1994; Shea et al., 2011). ABP peaks at the end of the subjective activity period, whereas the phase of its trough is less consistent (Shea et al., 2011). The amplitudes of the circadian rhythms of HR and, particularly, of ABP in subjects under unmasking conditions (Krauchi and Wirz-Justice, 1994; Shea et al., 2011) are approximately one third to one half of those for subjects in real-life conditions, who experience day-night changes in wake-sleep behavior and light-dark exposure (Staessen et al., 1997).

These data indicate that although circadian rhythms of autonomic variables directly contribute to the day-night differences in ABP and HR, such direct contribution is limited compared to that of day-night differences in wake-sleep behavior. However, as discussed in Section 3.3, the day-night differences in wake-sleep behavior are themselves under circadian control. It follows that the wake-sleep behavior may be considered as a key intermediate mechanism of the circadian control of the CV system (Fig. 1). A similar conclusion has been reached by experimental studies on mice (Bastianini et al., 2012; Sheward et al., 2010) (Fig. 2). This conclusion also fits with the suggestion that the cessation of drinking during nocturnal sleep contributes to increase hematocrit and apparent blood viscosity by decreasing blood volume during the night (Talan and Engel, 1993; Talan et al., 1992; Touitou et al., 1986).

3.5. Day-night rhythms in light-dark exposure may mask the circadian autonomic control of the CV system

A defining property of circadian rhythms is that they entrain to environmental stimuli (Zeitgeber), the most important of which is the 24-h' cyclic variation of ambient light consequent to Earth's rotation (Roenneberg and Merrow, 2016). The master circadian oscillator in the SCN is entrained to the rhythm of retinal light exposure through the specialized retino-hypothalamic tract (Benarroch, 2011) (Fig. 1). Photic entrainment of the SCN clock is reinforced owing to SCN-driven regulation of melatonin release by the pineal gland. Melatonin release is strongly suppressed by the SCN in response to retinal light exposure, and shows a SCN-dependent circadian rhythm that peaks during the subjective rest period in humans. Melatonin acts back on SCN neurons, eliciting molecular changes that are opposite to those caused by retino-hypothalamic tract terminals in response to retinal light exposure (Benarroch, 2008). Melatonin also exerts distinct CV effects, including a decrease in nocturnal ABP in human subjects (Baker and Kimpinski, 2018; Cagnacci et al., 2005; Grossman et al., 2011). The mechanisms of these melatonin effects are still debated, as a vast array of cell types in addition to SCN neurons express melatonin receptors (Benarroch,

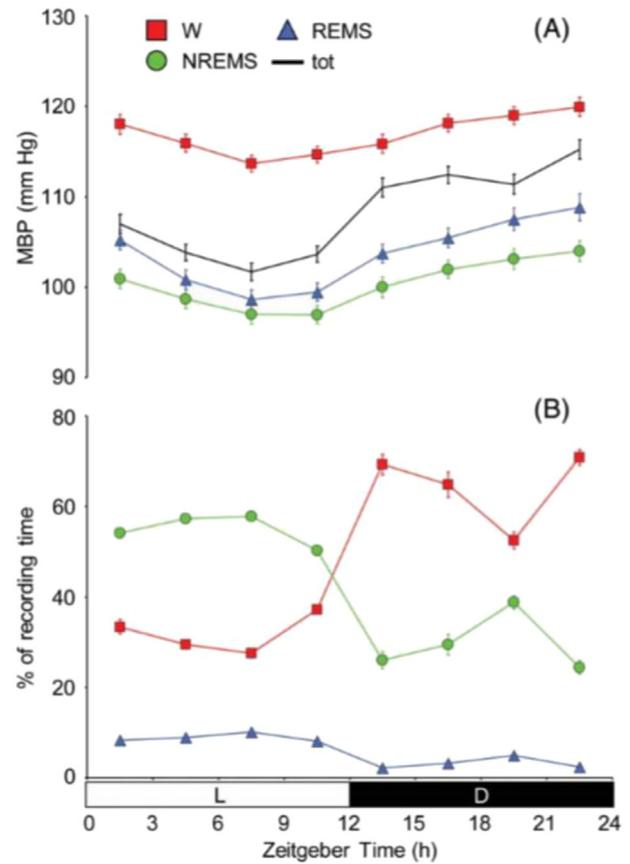


Fig. 2. The wake-sleep states are an important intermediate mechanism of the circadian control of arterial blood pressure.

Panels A and B show values (mean \pm SEM, $n = 26$) of mean blood pressure (MBP) and of the time spent in each wake-sleep state (W, wakefulness; NREMS, non-rapid-eye-movement sleep; REMS, rapid-eye-movement sleep), respectively, averaged over 3-h bins in C57Bl/6 wild-type mice. At variance with adult human subjects, mice spontaneously cycle between W, NREMS, and REMS throughout the light (L) – dark (D) cycle. A circadian rhythm entrained to the L-D cycle increases the probability of NREMS and REMS during the L period and the probability of W during the D period. The values of MBP measured regardless of the wake-sleep states (tot) show a L-D rhythm that peaks during the D period. A minor fraction of this rhythm's amplitude can be explained by the circadian rhythm of MBP that is evident in each wake sleep state (cf. the synchronous peaks and troughs of the red, green, and blue curves in panel A). However, the greater fraction of the MBP rhythm amplitude is due to the effects of wake-sleep states on MBP (cf. the y-axis offset between the red, green, and blue curve in panel A) combined with the L-D rhythm of wake-sleep states (panel B). This suggests that the wake-sleep states are an important intermediate mechanism of the circadian control of MBP. Reproduced from Bastianini et al., 2012, with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2008). However, a clear-cut circadian rhythm of ABP occurs in C57Bl/6 mice (Bastianini et al., 2012) (Fig. 2), which carry a spontaneous mutation that dramatically decreases melatonin production (Kasahara et al., 2010). This suggests that the circadian rhythm of melatonin release is not necessary for the occurrence of the circadian rhythm of ABP. Finally, light may exert masking effects on physical activity (Minors and Waterhouse, 1989; Mrosovsky, 1999) and HR (Thompson et al., 2008) in animal models. However, the extent to which these results are translatable to human subjects is presently unclear.

3.6. Circadian rhythms in CV and renal tissue cells modulate the circadian control of the CV system

3.6.1. The master circadian oscillator in the SCN entrains other cell-autonomous circadian oscillators

Cell-autonomous circadian clocks have been reported in almost every cell type studied, including hematopoietic stem cells (Méndez-Ferrer et al., 2008), cardiomyocytes (Beesley et al., 2016), and cells in blood vessels (Anea et al., 2018) and kidneys (Johnston and Pollock, 2018). This multitude of peripheral oscillators is entrained by the master SCN oscillator (Roenneberg and Merrow, 2016) by means of an as-yet poorly understood interplay of sympathetic nervous (Méndez-Ferrer et al., 2008), humoral (Mukherji et al., 2015), and energy-balance related (Oishi et al., 2017) cues, which are referred to as *eigen-Zeitgeber* (Fig. 1). Circadian rhythm entrainment and synchronization are not synonyms, as it is sufficient to have the same average period and a constant phase difference for two rhythms to be entrained (Johnson et al., 2003). Proteins involved in the core molecular clock machinery in the entrained peripheral clocks typically act as transcription factors for other genes, including non-clock related genes. As a result, a substantial portion of the transcriptome and proteome of peripheral oscillators undergoes a circadian rhythm (Doherty and Kay, 2010; Luck et al., 2014).

3.6.2. CV effects of intrinsic circadian rhythms of cardiomyocytes

Evidence obtained on mice with circadian clock mutations restricted to the heart suggests that the intrinsic cardiomyocyte clock is responsible for part of the difference in HR values between the active and rest periods of the day, which correspond to the nighttime and daytime, respectively, in mice (Bray et al., 2008). Conversely, day-night difference in ABP are fully preserved in mice with cardiomyocyte-specific impairment of the circadian clock (Bray et al., 2008; Xie et al., 2015). Thus, the contribution of the cardiomyocyte clock to the day-night rhythms of CV variables may be relatively small and limited to HR.

On the other hand, the intrinsic cardiomyocyte clock exerts powerful effects on cardiac metabolism (Durgan and Young, 2010). In particular, the cardiomyocyte clock enhances cardiac glucose oxidation and triglyceride and glycogen synthesis during the active period, and enhances cardiac protein synthesis and autophagy at the beginning of the rest period (Young, 2016). These circadian rhythms may act to fine-tune at the cardiac tissue level the strong circadian regulation of whole-body carbohydrate, protein, and lipid metabolism (McGinnis and Young, 2016). During the active period, these circadian effects anticipate the increased cardiac work due to physical activity and improve the effectiveness of cardiac storage of nutrients obtained through foraging and eating. At the beginning of the rest period, conversely, these circadian effects concentrate cardiac growth and repair processes at a time when the cardiac work is anticipated to be low (Young, 2016).

3.6.3. CV effects of intrinsic circadian rhythms of cells in blood vessels

Intrinsic circadian clocks have been demonstrated in the endothelial, smooth muscle and fibroblast cellular components of the vessel wall (Anea et al., 2018; Paschos and FitzGerald, 2010). Although direct proof is lacking, the operation of these vascular clocks may explain why nitric oxide production by the endothelial nitric oxide synthase (eNOS) and the vasodilatory response of rat mesenteric arteries to acetylcholine are lower during the rest period than during the active period (Denniff et al., 2014), and so is the vasodilatory response of rat cerebral blood vessels to ATP (Durgan et al., 2017). Conversely, the contractile responses of endothelium-denuded mesenteric and renal arteries in wild-type mice and the increases in ABP consequent to intravenous phenylephrine infusion are higher during the rest period than during the active period in mice (Denniff et al., 2014; Masuki et al., 2005; Xie et al., 2015) (Fig. 2). The increased vascular contractile activity during the rest period in mice has been linked to an increase in the activity of Rho kinase in vascular smooth muscle, which is driven by

the intrinsic circadian clock and inhibits the dephosphorylation of the regulatory myosin light chain (Saito, 2015; Xie et al., 2015). The issue of whether Rho kinase modulation of actomyosin contractility in vascular endothelial cells (Huvneers et al., 2015) undergoes a similar circadian rhythm still awaits investigation.

Overall, these findings appear counterintuitive, given that ABP shows a robust circadian rhythm with *lower* values during the rest period than during the active period (Bastianini et al., 2012; Xie et al., 2015). The intrinsic vascular clock would thus seem to drive day-night rhythms of vascular contractility and response to vasoconstrictors and vasodilators that compensate, in part, for those in SNA, blood volume, and ABP. Mutant mice with disrupted circadian clock in vascular smooth muscle cells were recently found to have reduced amplitude of the day-night rhythm of ABP values compared to control mice. Paradoxically, however, this occurred because of a decrease in ABP during the active period, while ABP values during the rest period were similar to those of control mice (Xie et al., 2015). The mechanisms underlying this mismatch still remain to be investigated, and may well include indirect humoral and reflex circuits that control the CV system.

3.6.4. CV effects of intrinsic circadian rhythms of kidney cells

Circadian molecular clocks have been reported in renal glomerular capillaries, proximal tubule, thick ascending limb of Henle's loop, distal loop, and collecting duct (Johnston and Pollock, 2018). The available evidence is thus consistent with a pervasive role of circadian rhythms in modulating kidney function (Johnston and Pollock, 2018; Solocinski et al., 2017). This modulation may reverberate on day-night CV rhythms due to its impact on sodium and water balance and, therefore, on cardiac preload and effective circulating volume. At present, however, evidence that this may happen is only suggestive. In mice, in particular, activity of the thiazide-sensitive sodium and chloride cotransporter (NCC) in the distal tubule is higher during the active period than during the rest period as a result of post-translational modifications entrained by the glucocorticoid rhythm. Interesting, disruption of the circadian glucocorticoid rhythm by chronic corticosterone infusion increases NCC activity during the rest period and results in a blunted ABP dipping pattern (Ivy et al., 2016). Medications used by patients with CVD, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone agonists, also alter renal function and may therefore interact with, or even potentially modify, the intrinsic circadian rhythms of kidney cells.

3.7. Summary of physiological mechanisms of day-night autonomic and hemodynamic rhythms

In human subjects in real-life conditions, circadian rhythms coordinated by the SCN ensure that most of the daytime is spent in wakefulness and with bright light exposure, and that most of the nighttime is spent in sleep in darkness or with dim light exposure. Direct circadian effects, elicited either by the master SCN oscillator by means of hormonal, autonomic, and metabolic mechanisms, or by local circadian clocks in the heart, blood vessels, and kidneys, play a role in modulating the day-night rhythm of CV activity. The day-night rhythm of light exposure may impact on the day-night hemodynamic rhythms primarily by entraining the SCN circadian oscillator, and, secondarily, by suppressing melatonin. However, the main circadian contribution to the day-night rhythm of ABP and HR is indirect, and mediated by changes in wake-sleep behavior. Day-night changes in wake-sleep behavior thus represent the main intermediate mechanisms of the circadian control of the CV system. Perturbation of this mechanism by sleep-related disorders may thus significantly alter day-night rhythms of CV variables.

4. Effects of common sleep-related disorders on nighttime CV activity, atherosclerosis burden, and risk of CVD events

4.1. Obstructive sleep apnea

OSA is a condition characterized by repeated partial or complete obstruction of the upper airways during sleep. OSA is highly prevalent in the general population, with figures ranging from 6%–17% up to 49% in aged subjects, even with a relatively conservative threshold of ≥ 15 apneas or hypopneas per hour (Senaratna et al., 2017). Nevertheless, data on the prevalence of a high nocturnal ABP in patients with OSA are still surprisingly scanty (Torres et al., 2015). Because of the repeated CV changes associated with apneas and summarized in Section 3.2, OSA is associated with increased nighttime variability of ABP and a blunted ABP dipping pattern (Marrone and Bonsignore, 2018). A recent study even reported that the occurrence of higher values of ABP during the nighttime than during the daytime is independently associated with OSA (Genta-Pereira et al., 2018). On the other hand, OSA has been linked to atherosclerosis burden in some (Gunnarsson et al., 2014; Kent et al., 2013), but not all (Kim et al., 2017) studies. A positive association has been confirmed by different systematic reviews and meta-analyses, particularly in patients with long-standing and severe OSA (Ali et al., 2014; Nadeem et al., 2013; Zhou et al., 2017). Finally, OSA is strongly associated with a number of CVD, including stroke, myocardial infarction, and sudden cardiac death (Javaheri et al., 2017). OSA during REM sleep may be particularly associated with a blunted ABP dipping pattern, although the mechanisms of this association and its consequences on increased CVD risk are still unclear (Varga and Mokhlesi, 2018). In animal models, the pro-arrhythmic effects of OSA can be attenuated by renal sympathetic denervation, indicating that they significantly depend on enhanced renal efferent SNA and/or afferent nerve activity (Linz et al., 2018). Moreover, OSA patients show augmented cardiorespiratory and sympathetic responses to acute hypoxia. These enhanced responses are attributed to an enhanced carotid body chemoreflex, itself a potential result of chronic intermittent hypoxia (Iturriaga, 2018). Taken together, these data indicate a massive dysregulation of SNA in patients with OSA. This dysregulation might contribute to circadian desynchrony, given that, as mentioned in Section 3.6.1, SNA is one of the eigen-Zeitgeber whereby the master SCN clock entrains peripheral circadian rhythms.

4.2. Insomnia

Insomnia is a condition characterized by difficulties initiating or maintaining sleep or by early morning awakening associated with impaired daytime functioning. Insomnia is a high-prevalence disorder, affecting 6%–19% of subjects in different European countries (Riemann et al., 2017). As was the case for OSA, information on nocturnal ABP values in patients with insomnia is very limited (Jarrin et al., 2018). The available evidence, based on a single study, indicates that chronic insomnia entails higher nighttime ABP values (Lanfranchi et al., 2009). Information on the association of insomnia with atherosclerosis burden is also limited (Aziz et al., 2017). This association was reported by two studies on elderly Japanese subjects (Nagai et al., 2013; Nakazaki et al., 2012), but not by a previous study on an inter-ethnic subject sample in the U.S.A (Ramos-Sepulveda et al., 2010). Nevertheless, a meta-analysis of 13 prospective studies published before 2012 concluded that insomnia increases by 45% the risk of developing and/or dying from CVD (Sofi et al., 2014), and a more recent study on over 44,000 subjects from Taiwan reported that insomnia is associated with almost two-fold incidence of myocardial infarction and stroke (Hsu et al., 2015).

4.3. Restless legs syndrome and frequent periodic leg movements during sleep

The restless legs syndrome (RLS) is a neurological sensorimotor

disease characterized by an urge to move the legs often associated with unpleasant sensations in the legs. This urge and the accompanying sensations begin or worsen during periods of rest or inactivity, particularly in the evening or at night, and are temporarily relieved by movement (Allen et al., 2014). The prevalence of RLS in the general adult population is approximately 2%–5% with the strictest estimation criteria (Ohayon et al., 2012). While disturbances of sleep onset and/or maintenance are not among the diagnostic criteria for RLS, they are recognized as common and distressing for RLS patients, and are included among the features to be considered for a comprehensive diagnostic assessment (Allen et al., 2014).

Periodic leg movements during sleep (PLMS) are motor phenomena characterized by a triple leg flexion (ankle, knee and hip, often bilateral) organized into sequences of four or more events separated by intervals of 10–90 s (Ferri et al., 2016). The presence of frequent PLMS is extremely common in RLS patients, and is included among the clinical features supporting the RLS diagnosis (Allen et al., 2014). A high occurrence rate of PLMS ($> 15/h$) per se is also highly prevalent in the general population, with three recent studies reporting prevalence figures between 25% and 36% (Haba-Rubio et al., 2016; Leary et al., 2018; Szentkiralyi et al., 2018). Once again, information on the nocturnal values of ABP in patients with RLS and/or frequent PLMS is still limited. The available evidence indicates that RLS is associated with a blunted ABP dipping pattern (Erden et al., 2012; Sieminski and Partinen, 2016) and with higher nighttime values of ABP (Sieminski and Partinen, 2016). There is also evidence that nighttime ABP variability is enhanced by frequent PLMS in patients with RLS (Cassel et al., 2016), and that frequent PLMS are associated with nocturnal hypertension, at least in children (Wing et al., 2010). Quite surprisingly, information on the link between RLS and/or frequent PLMS and atherosclerosis burden is extremely limited, with one study unexpectedly reporting lower values of the carotid intima-media thickness in patients with idiopathic RLS than in control subjects (Park et al., 2012).

The association between RLS, frequent PLMS, and CVD risk is debated. A large study published in 2008 concluded that RLS is significantly associated with CVD, and that the association is stronger in subjects with greater frequency or severity of RLS symptoms (Winkelman et al., 2008). Conversely, two systematic reviews of papers published before 2017 did not report evidence for an increased risk of cerebrovascular and CVD events in RLS patients (Katsanos et al., 2018; Kendzerska et al., 2017). However, one of these reviews did conclude that frequent PLMS may be a prognostic factor for incident CVD events (Kendzerska et al., 2017). The picture changed again with two studies published in 2017 and 2018, which indicated that RLS and frequent PLMS are significantly associated with incident myocardial infarction (Winkelman et al., 2017), and that RLS entails a significantly higher risk of CVD mortality (Li et al., 2018).

4.4. Summary of the effects of OSA, insomnia, RLS, and frequent PLMS on nighttime CV activity, atherosclerosis burden, and risk of CVD events

The limited available evidence highlights the need for focused research on the CV correlates of OSA, insomnia, RLS, and frequent PLMS. Nonetheless, recent evidence does suggest that these highly prevalent sleep-related disorders entail increased nighttime CV activity, increased atherosclerosis burden (at least with OSA and insomnia), and increased CVD risk.

5. The links between nocturnal ABP values, atherosclerosis burden, and the risk of CVD events

5.1. Higher nocturnal ABP values increase CVD risk

A study published in 2003 on patients with treated hypertension reported that higher nighttime values of systolic ABP were associated

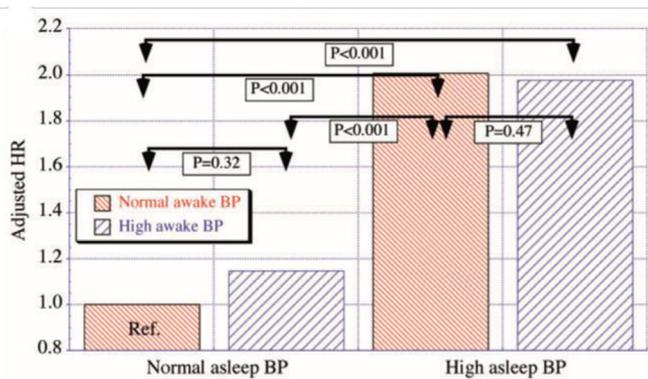


Fig. 3. Arterial blood pressure during nighttime sleep is an important determinant of the risk of cardiovascular disease events.

The graph summarized results of the prospective evaluation of 18,078 individuals with baseline ambulatory blood pressure (BP) ranging from normotension to hypertension. The cardiovascular disease (CVD) outcome in this study was the composite of CVD-related death, myocardial infarction, coronary revascularization, heart failure, ischemic stroke, and hemorrhagic stroke. HR, hazard ratio. The asleep systolic BP/diastolic BP mean was considered normal if $< 120/70$ mmHg, and high otherwise. Ref., reference group for HR calculations. The *P* values refer to the statistical comparisons between the groups indicated by arrowheads. Reproduced from Hermida et al., 2018, with permission.

with increased risk of CVD events after adjustment for classic risk factors including office measurements of ABP (Clement et al., 2003). This finding was essentially replicated in later studies on patients with chronic kidney disease (Minutolo et al., 2011), and on subjects who were normotensive during the daytime (Fan et al., 2010). The predictive accuracy of nighttime ABP for CVD events was found to be better than that of daytime ABP by four large studies (Boggia et al., 2007; Dolan et al., 2005; Fagard et al., 2008; Roush et al., 2014), although in one of these (Boggia et al., 2007), this primacy of nighttime ABP was limited to the prediction of fatal CVD events.

There is evidence supporting causality of the link between high nighttime ABP and CVD events. In the MAPEC study results published in 2011, the average ABP during the nocturnal sleep time was the most significant prognostic marker of CVD morbidity and mortality (Hermida et al., 2011). Causality was suggested by the finding that the most important predictor of CVD event-free survival was the decrease in the average ABP during nighttime sleep, which was achieved by taking antihypertensive treatment at bedtime rather than upon morning awakening (Hermida et al., 2011). This conclusion was supported in 2018 by the results of the Hygia project (Hermida et al., 2018) (Fig. 3).

5.2. Higher nocturnal ABP values are associated with increased atherosclerosis burden

A non-dipping pattern of ABP and the occurrence of nocturnal hypertension have been associated with increases in the carotid intima-media thickness in a middle-aged population from Finland (Vasunta et al., 2012). More recently, a non-dipper ABP pattern has also been associated with carotid plaques in hypertensive subjects whose ABP values were within the normal range after treatment (Gao et al., 2017), and with coronary artery calcification in patients with chronic kidney disease (Choi et al., 2017). In the presence of nocturnal hypertension, ABP dipping entails a similar subclinical cardiac and extra-cardiac organ damage as ABP non-dipping (Cuspidi et al., 2012). On the other hand, in newly diagnosed hypertensive subjects, nocturnal hypertension, but not ABP non-dipping, is associated with subclinical atherosclerosis and structural abnormalities of the left ventricle (Androulakis et al., 2015). The occurrence of high nocturnal ABP values may thus mediate, at least in part, the link between a non-dipping ABP pattern

and the atherosclerosis burden. Increased nighttime variability of ABP and increased nighttime values of HR may also contribute to subclinical CV organ damage (Cuspidi et al., 2018; Stamateopoulos et al., 2010).

6. Sleep-related disorders may increase atherosclerosis burden and the risk of CVD events by increasing nighttime CV activity

6.1. Sleep-related disorders may increase the nighttime incidence of CVD events by causing large increases in nighttime CV activity

Sleep-related disorders may increase the occurrence of CVD events by causing increases in nighttime CV activity large enough to convert the nighttime sleep period from a period of relative protection against CVD events (Marler et al., 1989; Mulcahy et al., 1988; Muller et al., 1989; Reavey et al., 2013; Willich et al., 1987) to one of enhanced risk. In particular, the wide and repeated CV fluctuations associated with apneas during the night in subjects with OSA may provide conditions of significant hemodynamic stress and autonomic activity, favoring vulnerable plaque rupture and malignant arrhythmias (Somers et al., 1995). In patients with OSA, indeed, the distribution of CVD-related deaths throughout the 24 h is virtually flat (Martins et al., 2017), whereas the distribution of sudden death from cardiac causes peaks during the sleeping hours (Gami et al., 2005). Similar phenomena might be driven by the CV changes that accompany frequent PLMS, particularly in patients with RLS (Cassel et al., 2016). However, information on the day-night distribution of CVD-related death in general and of sudden cardiac death in particular is lacking in patients with RLS and/or frequent PLMS. Incidentally, this information is lacking in patients with insomnia as well.

6.2. Sleep-related disorders may increase atherosclerosis burden and the risk of CVD events by increasing CV activity at a time when circadian rhythms anticipate CV rest

A different, non-alternative hypothesis is that nocturnal increases in CV activity are particularly dangerous for CV health because they challenge the CV system at a time when it is anticipating reduced activity due to circadian rhythms. At such a wrong time, even increases in CV activity that are not so dramatic as to trigger plaque rupture might powerfully promote subclinical cardiac damage and atherosclerosis burden, thereby ultimately enhancing the risk of CVD events, particularly upon morning awakening (Fig. 4).

As discussed in Section 3.6.2, there is evidence that the cardiomyocyte circadian clock concentrates cardiac growth and repair processes at the beginning of the rest period, when the cardiac workload is anticipated to be low. It is thus conceivable that an increase in cardiac activity represents a more powerful stimulus to cardiac hypertrophy during the subjective rest period than during the subjective active period, which correspond to the nighttime and the daytime, respectively, for humans entrained to real-life light-dark cycles. There is, indeed, some evidence in support of this hypothesis. One set of experiments involved rats with renovascular hypertension subjected to varying regimens of anti-hypertensive treatment with captopril, an inhibitor of the angiotensin converting enzyme. In these rats, the best predictor of the cardiac hypertrophy response was the ABP value during the first half of the rest period (Morgan et al., 2000). A different set of experiment on wild-type mice demonstrated that a week's period of administration of isoproterenol, a non-selective beta adrenoceptor agonist, caused significant cardiac hypertrophy when isoproterenol was administered at the start of the rest period, but not when it was administered at the start of the active period. This diurnal variation in the cardiac hypertrophic response to isoproterenol did not occur in mice with mutations that impaired the cardiomyocyte circadian clock (Durgan et al., 2011).

Circadian rhythms may also make the vasculature abnormally reactive to increased CV activity during the subjective rest period,

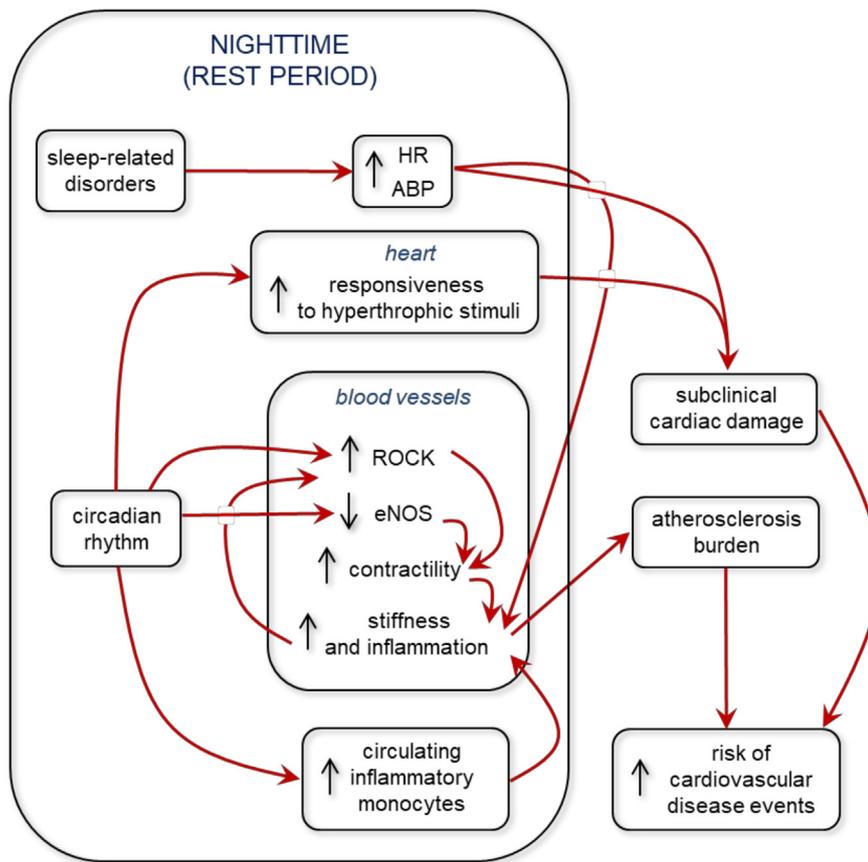


Fig. 4. Conceptual framework of the hypothetical mechanism whereby sleep-related disorders may increase cardiovascular disease risk by increasing nighttime cardiovascular activity.

HR, heart rate; ABP, arterial blood pressure; ROCK, Rho kinase; eNOS, endothelial nitric oxide synthase. See the text and particularly Section 6.2 for details.

ultimately leading to increased atherosclerotic burden. During the rest period, as discussed in Section 3.6.3, increased Rho kinase activity increases the vascular smooth muscle contractility (Saito, 2015; Xie et al., 2015), while decreased eNOS activity decreases the vascular reactivity to vasodilators (Denniff et al., 2014). Increased Rho kinase activity and decreased eNOS activity may be part of a positive feedback molecular network, which amplifies the increases in vessel wall stiffness resulting from mechanical signals, such as those that may arise from increased ABP (Huvneers et al., 2015). The occurrence of localized increases in vascular stiffness during the nighttime may also potentiate vascular inflammation (Huvneers et al., 2015), contributing to the development of atherosclerotic lesions (Raggi et al., 2018). In particular, local increases in vascular stiffness may stimulate rolling leukocytes to spread on the apical endothelial surface (Wojciak-Stothard et al., 1999). Leukocyte spreading is thought to favor their crawling and locating a path of least resistance (Huvneers et al., 2015), through which they may eventually cross the endothelial barrier by diapedesis (Martinelli et al., 2014). In turn, integrin-mediated leukocyte adhesion to the vascular endothelium may trigger Rho-mediated increases in vascular stiffness, thus initiating a positive feedback loop (Huvneers et al., 2015).

The deleterious effects of this loop for the development of atherosclerotic burden may be amplified during the nighttime by circadian mechanisms that involve the immune system (McAlpine and Swirski, 2016) (Fig. 4). The spleen, lymph nodes, and peritoneal macrophages of mice contain intrinsic circadian molecular clockwork that regulates > 8% of their transcriptome (Keller et al., 2009). Circulating hematopoietic stem cells and their progenitors exhibit robust circadian fluctuations, peaking during the subjective rest period, and being entrained by adrenergic signals delivered by autonomic nerves to the bone marrow (Méndez-Ferrer et al., 2008). Hematopoietic stem and progenitor cells progressively relocate from the bone marrow to the spleen, where they expand and differentiate to inflammatory Ly-6C^{high} monocytes. These monocytes then intravasate, circulate, and accumulate in

atherosclerotic plaques (Robbins et al., 2012). The Ly-6C^{high} monocytes in the blood and spleen exhibit circadian clock-driven circadian variations that peak during the subjective rest period, and which are accompanied by corresponding increases in their recruitment to spots of inflammation (Nguyen et al., 2013).

7. Conclusions

The evidence discussed in this review suggests that the links between sleep and CVD risk depend on time scale. The physiological decreases in ABP and HR and the increase in parasympathetic cardiac modulation during non-REM sleep make the nighttime a period of relative protection from CVD events, at least in comparison to the early morning hours. High-prevalence sleep-related disorders such as OSA, insomnia, and RLS disrupt the physiological effects of sleep on CV control. This disruption may be severe enough to convert the nighttime sleep period from one of relative protection from CVD events to one of relative risk. During the night, persistent mismatch between the increase in CV activity due to sleep-related disorders and the decrease in CV activity anticipated by circadian rhythms may increase atherosclerosis burden, and, ultimately, the risk of CVD events during the daytime (Fig. 4).

8. Perspectives

A number of critical details are still missing. The neurophysiological and hemodynamic mechanisms of the physiological sleep-related decrease in ABP during the nighttime are still largely unknown, for instance concerning the relative roles of decreases in cardiac output and total peripheral resistance. The mechanisms whereby the master circadian clock in the SCN entrains the different peripheral molecular clocks, such as those in the cardiac and vascular cells, are still unclear. These mechanisms might represent druggable targets to decrease CVD

risk. The specific role of the intrinsic circadian clocks in vascular smooth muscle and renal tubular cells in the day-night rhythm of ABP also deserves further targeted investigation. Detailed data on the 24-h distribution of CVD events and particularly of sudden cardiac death are lacking for patients with insomnia, RLS, and frequent PLMS. There is need for large-scale studies with ambulatory ABP monitoring on the effects of these sleep-related disorders on the day-night rhythms of ABP and HR. The association between insomnia, RLS, and frequent PLMS with markers of atherosclerosis burden demands further studies, taking into account nocturnal values of ABP and HR in addition to other CVD risk factors and the severity and duration of sleep-related disorders. These are critical issues, as treatment of sleep disorders could at least partly modify the picture by restoring sleep and circadian physiology. Careful exploration of casual pathophysiological links employing the power of preclinical animal models will be ultimately key to prove that increased CV activity during the night represents a final common mechanism linking sleep disorders to CVD risk.

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