Circadian control of human cardiovascular function

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Abstract

Endogenous circadian rhythms prepare the cardiovascular (CV) system for optimal function to match the daily anticipated behavioral and environmental cycles, including variable activities when awake during the day and recuperation when sleeping at night. The overall day-night patterns in most CV variables result from the summation of predictable circadian effects with variable behavioral and environmental effects on the CV system. The circadian system has also been implicated in the morning peak in the incidence of adverse CV events, including myocardial infarction, stroke, and sudden cardiac death. We discuss the resting and stress-reactive circadian control of CV physiology in humans and suggest future research opportunities, including improving CV therapy by optimally timing therapy relative to a person's internal body clock time.

2 Introduction

Using rigorous experimental protocols in humans[1] *endogenous* circadian rhythms have been discovered in numerous variables that can influence overall CV function. For instance, rhythms in cortisol, BP, heart rate, and autonomic function persist independent of the effects

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9 Declaration of interest
Nothing declared

[1]Throughout this review we refer to the "circadian" as being driven by the internal body clock (i.e. endogenous), independent of the effects of the environment or behaviors. Until researchers begin to use this term consistently it is advisable to read the protocols of all studies in this area for appropriate data interpretation. For example, many studies report differences in CV variables and CV pathophysiology across the day and the night without controlling for variable behaviors and environmental changes across the 24-hours, such as temperature, meal intake, physical activity, and sleep. Such 24-hour CV patterns have often been described as 'circadian' variations even though these studies have generally not assessed the endogenous nature of this variability. We use the term 'circadian clock' to infer the molecular clocks centrally in the suprachiasmatic nuclei and in the peripheral cells and tissues.

of daily environmental and behavioral cycles, such as the daily light/dark, wake/sleep, activity/rest, and eating/fasting cycles[*1–3]. These endogenous circadian rhythms have evolved to optimize function based on anticipated daily environmental and behavioral cycles, and based on the assumption that being physiologically prepared to respond to an anticipated stressor is advantageous compared to waiting for the stressor to occur and then reacting. For instance, cortisol increases are very sluggish in response to an acute stress, whereas the circadian system (the individual or summated functional effects of the central and peripheral clocks) increases cortisol well before the anticipated wakening in the morning, which 'primes the pump' for rapid CV adaptation to maintain homeostasis in the face of rapid changes in posture and increased physical activity immediately upon awakening [4]. In addition to preparing us for the anticipated exposure to variable mental and physical stresses during the day, the circadian system also serves to optimize our CV physiology for the anticipated habitual schedule of resting, recuperation, repair, and preparation during the night. In animal models, the peripheral circadian clock in the cardiomyocyte has been shown to facilitate myocardial processes of contractility, gene expression and metabolism, and tolerance to ischemia reperfusion injury [5–7]. On a continuous basis, the endogenous rhythms of resting CV physiology and CV recuperation summate with the CV responses to common behaviors and environmental changes across the day and night and lead to the characteristic day-night patterns in CV physiology (Figure 1, for BP).

There are substantial day/night patterns of adverse cardiovascular (CV) events, such as myocardial infarction and stroke, with most epidemiological studies in the general population detecting peak incidence in the morning [8–11]. The role of circadian system has been studied as a potential factor playing a role in these day/night patterns primarily because many CV variables such as blood pressure (BP) and markers of hemostasis abruptly increase in the morning hours when vascular endothelial function (VEF) is attenuated [12–17]. As explained in section 5, there is now proof that the morning rise in some of these markers is driven by the circadian system, whereas some markers are more affected by behaviors. Theoretically, the same endogenous rhythms that are advantageous in healthy humans, may however, be perilous in vulnerable individuals, e.g., people with underlying CV disease, and can lead to an increased risk for adverse CV events at specific times of day (Figure 2).

Here we briefly review: 1) the hierarchy of circadian control, and 2) endogenous circadian rhythms in CV variables under both resting and stressed conditions. We then discuss the role of the circadian system in CV disease and highlight areas for future work, including studying people with existing CV disease and the potential to improve clinical outcomes by timing therapies to specific circadian phases.

3 Hierarchy of circadian control

In mammals, the central circadian clock is located in the suprachiasmatic nucleus in the anterior portion of the hypothalamus and is primarily entrained to the 24-hour environmental cycles (e.g., as seasons change) by light cues via the retino-hypothalamic tract. Peripheral circadian clocks also exist throughout the organism from the cell to the organ level. These peripheral clocks work on a transcription-translation negative feedback network wherein

clock genes facilitate the translation of proteins, which in turn repress the clock genes, a cycle that takes ~24 hours. While all peripheral clocks can cycle even in the absence of inputs from the suprachiasmatic nucleus [18,19], this central clock helps to synchronize all peripheral circadian clocks via neural, hormonal, and systemic pathways [20] [21] and body temperature [22]. Circadian clocks across the CV system, including the heart, the vasculature, the kidney and the autonomic nervous system [20] [23–25] affect resting CV variables, their responsivity to stresses during the day and CV system's ability to rest and recuperate at night.

4   Protocols to study the endogenous circadian system in humans

Separating the effects of behaviors from those of the endogenous circadian system, and ultimately studying the interaction between the two require rigorous multi-day laboratory protocols that schedule all behaviors (including sleep and wake) and control all environmental factors, including living in dim-light and time-isolation to avoid resetting the central circadian clock (please see Thosar et al. [26] for detailed illustrations of these protocols). One protocol is the 'constant routine' (CR) [27], in which participants live under conditions of constant wakefulness in a temperature-controlled suite in a semi-recumbent position for >24 hours. In an attempt to provide continuous nutrition while maintaining caloric balance, participants consume small identical iso-caloric meals, typically every hour, as opposed to three large meals per day. Circadian rhythms in CV function are then uncovered by making repeated measurements across >24 h [3,28,29]. One limitation of this constant routine protocol is that due to continued wakefulness, there is an accumulation of sleep loss, which could affect variables of interest. Nonetheless, in many instances, this effect is minimal compared to circadian variation and can be statistically accounted for [3,28,29]. A more sophisticated protocol, that can avoid sleep loss is called the 'forced desynchrony'(FD) [30], wherein behaviors and circadian rhythms are 'desynchronized' by scheduling participants to live on a non-24-hour 'day'. Standardized behaviors and physiological tests can then be evenly distributed across all phases of the circadian cycle. Using this method, it is possible to statistically separate the effects of all three components: behaviors, the circadian system, and their interactions. An underlying assumption of the FD is that in the dim light conditions, the circadian pacemaker 'free-runs' and synchronization between central and peripheral circadian clocks is preserved, as has been demonstrated for numerous physiological markers including melatonin, cortisol, core body temperature, and plasminogen activator-inhibitor 1 (PAI-1) [2,31,32].

5   Circadian rhythms in resting cardiovascular variables

5.1   Hemodynamic system

Blood pressure is higher during the day compared to the night [14,15]. Furthermore, BP immediately upon awakening is a predictor of adverse CV events [33,34] (also see [35] for race differences). Changes in common behaviors, including upright posture and physical activity, do not fully explain the day/night patterns in BP [36]. To test whether the circadian system contributes to the diurnal variation in BP, early studies using modified CR protocols and reported an absence of a circadian rhythm in BP [37,38]. However, the lack of strict

light and physical activity control confounded the interpretation of results. In contrast, Shea et al. studied healthy young adults (mean age 26y) in three separate circadian protocols (CR, 20-hour FD, and 28-hour FD) [3]. They discovered that the circadian rhythm in BP exhibited a trough in the early morning and a peak in the evening corresponding to ~8 PM suggesting that the circadian rhythm in BP is unlikely to play a role in morning peak in adverse CV events [39,40]. More recently, using a 5-hour 20-minute FD, Thosar et al. confirmed these results in midlife adults (mean age 51y) [1], although the circadian phase for the peak in BP was advanced by ~2 hours compared to the previous report [1]. These authors also failed to find a circadian rhythm in heart rate [1]. Aging can alter the circadian rhythms in melatonin, body temperature, and cortisol [41–43], and it is possible that aging alters circadian CV rhythms in midlife participants, and this ought to be studied further due to the potential clinical significance.

5.2 Autonomic nervous system

The autonomic nervous system is an important regulator of a multitude of CV processes. Using modified CR protocols, some studies have demonstrated that cardiac vagal activity is driven by the homeostatic sleep pressure [44], whereas others have concluded that it is driven by the circadian system [45–47]. In contrast, recent CR and FD protocols with tighter control of lighting, activity, and meal intake reported that both sympathetic and cardiac vagal tone at rest were both under circadian control and that basal sympathetic activity peaked around mid-day, whereas cardiac vagal activity peaked in the morning ~8 AM [2,48,49]. The circadian peak in the stress hormone cortisol was also around the time of awakening [2]. Together, these results suggest that the circadian trough in BP in the morning may be related to cardiac vagal tone, yet the circadian peak in BP appears to be unrelated to the circadian rhythms in autonomic nervous system activity. The aforementioned studies included different indirect indices of the autonomic nervous system including, cardiac inter-beat interval, pNN50, high-frequency power, and plasma levels of epinephrine and norepinephrine. Therefore, data must be interpreted while considering the strengths and weaknesses of each measurement. Use of the direct measurement of sympathetic neural activity (e.g., muscle sympathetic nerve activity) remains an area of opportunity in this field.

5.3 Renin-Angiotensin-Aldosterone system

Similar to the autonomic nervous system, the renin-angiotensin-aldosterone system is an important regulator of BP and systemic vascular resistance [50,51]. In humans, plasma renin activity and aldosterone have a day/night pattern with high levels early in the morning compared to the evening, and a longstanding observation has been that these morning increases in humans are due to prior nocturnal sleep [52,53]. More recently, these findings for aldosterone were revisited using two separate protocols: one to isolate the effects of nocturnal sleep while controlling the effects of the circadian system (e.g., dim light environment), and the second, a 5-hour 20-minute FD to identify any circadian rhythmicity. It was discovered that nocturnal sleep was not responsible for the morning rise in aldosterone, but rather, there is a robust circadian rhythm in aldosterone with a peak at the circadian phase corresponding to ~7 AM [*54]. Unfortunately, this study did not include measurement of plasma renin activity or high frequency measurements of sodium and potassium levels to aid clinical interpretation of these aldosterone data. Furthermore,

standard clinical assessment of aldosterone in hypertensive patients is performed in the morning, thus since the morning peak is driven by the circadian system, clinicians need to aware of any history of shift work or jet-lag in their patients before interpretation of their results [55].

5.4   Vascular endothelial function (VEF)

The vascular endothelium is a single layer of cells that lines the entire vascular network and performs functions that are critical to maintaining blood flow to vital organs [56,57]. In humans, VEF is relatively impaired in the morning [17,58] compared to other times of the day. Using two separate multi-day inpatient studies, which controlled for the effects of the circadian system, Thosar et al. [1,59] recently discovered that the morning impairment in VEF is due to the effects of the circadian system and not due to the effects of prior nocturnal sleep or the inactivity that typically accompanies sleep. In addition, mechanistic variables that affect VEF, namely endothelin-1 [60], and oxidative stress [61], both exhibited circadian rhythms with an increase across the morning hours and a peak around noon [1]. The morning increase in these biomarkers constitutes an increase in CV risk even though these markers' circadian peaks did not match the trough in VEF. These findings have important clinical implications in relation to adverse CV events, especially in people with existing CV disease who may have a concomitant surge in BP during the morning hours [62–64]. The next logical steps in this area are to study people with CV disease with a day night pattern of adverse symptoms (e.g., angina[65]) and to extend these findings to the coronary vasculature.

5.5   Hemostatic system

Blood clotting is a vital function to prevent excessive blood loss during injury, whereas fibrinolytic activity is antithrombotic and keeps blood vessels patent to ensure perfusion to organ systems. In humans, these factors display a day-night pattern with the greatest hemostatic activity occurring in the morning [13,66]. Using an FD protocol in healthy young adults, the increase in plasminogen activator inhibitor-1 (PAI-1) in the morning was found to be due to the effects of the circadian system [*67]. The magnitude of this circadian increase was several times larger than the increase in PAI-1 during exercise. In a similar FD study, the circadian system was found to cause a morning peak in platelet surface-activated GPIIb-IIIa, the final part of the platelet aggregation pathway [68]. These results demonstrate that the circadian system creates a pro-thrombotic milieu in the morning in healthy humans, which perhaps conferred some evolutionary advantage to prevent blood loss during morning activities [69]. However, in vulnerable individuals, this same circadian increase in hemostasis in the morning in the presence of other factors such as impaired VEF and the morning surge in BP could potentially trigger an adverse CV event (Figure 2).

6   Interacting effects on cv function of behaviors and the circadian system

The CV responses to all of the common behaviors (e.g., sleep and exercise) that we typically encounter across the day and night have been well-established. These CV responses to behaviors are superimposed on the basal circadian rhythms in CV physiology described above (Figure 1). Importantly, these behaviors could occur at any circadian phase; for

instance, emergency workers may be exposed to stresses at any time of day or night. Thus, it is important to determine the nature of these interacting effects, namely, are the behavioral and circadian CV effects simply additive, or are there more complex interactions (e.g., multiplicative). Moreover, the daily pattern of adverse CV events may be caused by these interactions. For instance, common behaviors such as arousal from sleep, a sudden change in posture, and an abrupt increase in physical activity during the morning could trigger adverse events at specific circadian phases in vulnerable individuals (Figure 2). Below, we consider how mild behavioral stresses interact with the circadian system when studied in constant environmental conditions. However, we must acknowledge that more robust stresses can occur in real life, and indeed that similar interactions may also occur between the circadian system and environmental stresses, such as heat and cold exposure. Moreover, all three may interact, which could be critically important, for instance, in susceptibility to heat exhaustion at specific times of the day. This is an area that needs to be studied in humans.

6.1   Circadian interactions with physical and mental stresses

Habitual physical activity is beneficial for CV and overall health, but in sedentary adults, physical exertion performed in the morning can increase the risk for adverse CV events [70]. Using a 20-hour FD in healthy humans to study the circadian reactivity of CV variables to exercise (60% of maximum heart rate for 15 minutes), it was discovered that the reactivity of BP and other CV markers to exercise is non-uniform across the circadian cycle [2,*71]. The increase in BP during exercise and BP recovery after exercise was the highest in the biological evening [2]. Conversely, the slowest recovery in BP occurred in the morning hours (~9 AM [71]), which could be related to the increased vasoconstrictor tone around that time [72]. Increases in plasma epinephrine and norepinephrine during exercise exhibited two large peaks at circadian phases corresponding to 07:00–10:30 and 20:00–22:00 [2]. Such ultradian rhythms have been demonstrated in cardiac β-adrenergic receptor density and function in animal models [73], and assessment of circadian changes in such receptor density would be valuable in humans. Moreover, the increase in plasma epinephrine from rest to exercise was twice as large at ~9 AM compared to ~5 AM [2]. Along with increased reactivity of the sympathetic nervous system, parasympathetic withdrawal during exercise was also the highest in the morning hours [2]. These same authors also discovered that the reactivity of epinephrine and norepinephrine to standardized mild mental stress peaked around noon. There was no statistical interaction between circadian phase and mental stress battery, but similar to exercise, sympathovagal balance in reaction to mental stress was significantly higher at ~9 AM [*74]. If such circadian effects of the autonomic nervous system to mental or physical stress persists in vulnerable people, it could explain the increased frequency of morning adverse CV events.

6.2   Circadian interaction with postural change

Most people get out of bed and stand up in the morning, yet this simple change in posture, after a prolonged period of recumbence across the night, is a large CV challenge that causes pooling of blood in the legs and significant compensatory changes in multiple CV variables [75]. To isolate the effects of posture alone, Hu et al. studied the circadian reactivity to passive postural change performed on a tilt table (moving from supine to 60° head-up for 15 min) [76]. Presyncope occurred in half of the healthy participants but almost exclusively

during the circadian phases corresponding to the biological night (22:30–10:30) [76]. This study uncovered a period of relative susceptibility to presyncope during the night when most people sleep, which could also explain why in the general population, the greatest likelihood of syncope occurs in the morning [77]. However, overnight vulnerability to syncope finding has implications for people who get out of bed frequently at night (e.g., parents of young children, elderly with nocturia) or people who are active at night (e.g., shift workers).

7 Clinical implications, future directions and conclusions

7.1 Circadian rhythms in people with existing cardiovascular disease

To begin to understand the clinical significance of circadian rhythms in CV function, Butler et al. have studied people with obstructive sleep apnea as these patients commonly experience adverse CV events in the middle of the night, unlike the morning risk in the general population [78] [79]. These authors discovered that central circadian clock markers such as cortisol and melatonin were not disrupted, but circadian rhythms in BP peaked much later in people with obstructive sleep apnea compared to healthy controls [*79]. Although the peak in the BP rhythm did not correspond to the commonly observed time of adverse CV events, this finding suggests that certain diseases could result in a shift in peripheral CV rhythms, with as yet unknown clinical consequences. In the area of CV surgery, it was recently discovered that aortic valve replacement surgeries scheduled in the morning carry a higher rate of mortality compared to afternoon surgeries [*80]. Furthermore, these authors performed an ex-vivo analysis of human myocardium revealing an endogenous time of day variation in ischemia-reperfusion tolerance which was attributed to increased expression of the nuclear receptor Rev-Erbα in the morning. Indeed, recent animal work suggests that Rev-Erbα is a mediator of clock-controlled processes such as mitochondrial function, metabolism, signaling, and contractile function in the heart [81]. A major research opportunity is to study people with existing CV disease who have either stable, or disrupted day-night patterns in CV physiology (e.g., people with angina [82] or non-dipping hypertension [83]).

7.2 Chronotherapy

Chronotherapy or time-based "circadian medicine" has been considered "Medicine in the fourth dimension"[84]. In the CV area, most large chronotherapy trials have targeted not the internal, but the external clock time, and most trials have focused on hypertension. For instance, the MAPEC trial of nearly 2,000 people with resistant hypertension showed that at least one anti-hypertensive medication consumed at bedtime, compared to all hypertensive medications in the morning, reduced the relative risk of all CV events and CV mortality by >60% during 5.6 years of follow-up [85]. The same authors conducted an even larger multi-center trial (HYGIA) of over 19,000 hypertensive patients [**86] and reproduced the MAPEC trial results. They discovered that evening dosing rather than upon awake dosing improved BP control and significantly diminished the occurrence of almost all adverse CV disease outcomes (relative risk 0.55, 95% CI[0.50–0.61]), including myocardial infarction and stroke. At the moment, there is a debate on the generalizability of the results in the HYGIA trial [87,88], along with a concern for inducing silent ischemia with nighttime medications [89]. A better understanding of sleep physiology and circadian rhythms in

people with hypertension will undoubtedly help to better interpret the results of future clinical trials. One hundred nineteen formulations on the World Health Organization's essential medicine list target products of rhythmic genes [90]. Furthermore, >50% of the top best-selling drugs in the US have short half-lives (<6 h required for the drug concentration to decrease to half of its initial dose) [90]. The next step is to conduct randomized controlled clinical trials to target medications, especially those with short half-lives, to match the peaks in endogenous circadian rhythms of physiology to maximize drug potency and avoid overmedication [91]. Targeting drug delivery based on internal circadian time will however, require the development of a more convenient circadian phase marker that can be used in the clinic. Commonly used circadian phase markers such as the dim-light melatonin onset, or cortisol measurements, which require numerous serial assays from samples taken while the patient remains in dim light (DLMO) in the laboratory or at home [*92,93], or continuous measurement of core body temperature are cumbersome and perhaps not suited for personalized medicine. Overall, circadian medicine has only been sporadically used in CV medicine across many decades (see [94] for a review). Yet, based on all the recent findings in circadian CV physiology, this area is now ripe for exploration to improve clinical outcomes and reduce side effects of drugs.

Acknowledgements:

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Highlights

The suprachiasmatic nuclei are the seat of the central circadian clock.

Peripheral circadian clocks exist throughout the cardiovascular (CV) system.

Together these clocks orchestrate resting and responsive rhythms in CV physiology.

Day-night CV patterns result from the summation of circadian and behavioral effects.

Timing drugs to specific circadian phases is a new opportunity to optimize therapy.
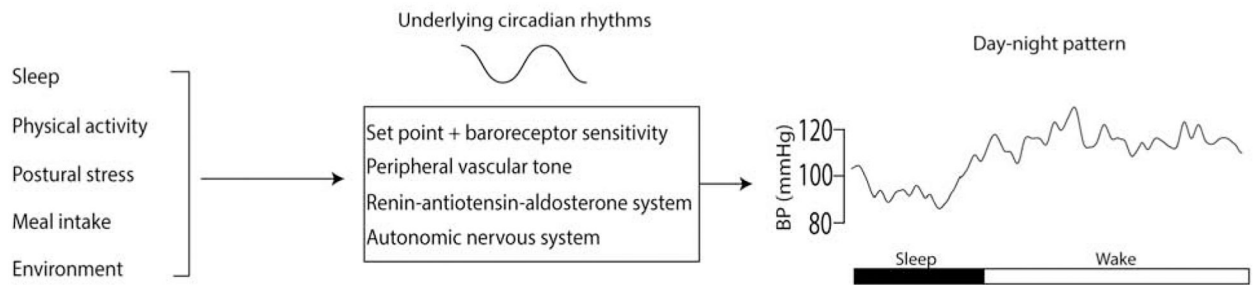
Figure 1. Day-night pattern in BP

In healthy individuals, BP has a characteristic day night pattern with an increase in BP upon awakening, and higher levels during the wake period compared to sleep. This day night pattern is a result of the composite effects of different behaviors and the environment, interacting with the underlying circadian rhythms in BP, peripheral vascular tone, renin-angiotensin-aldosterone system and the autonomic nervous system.
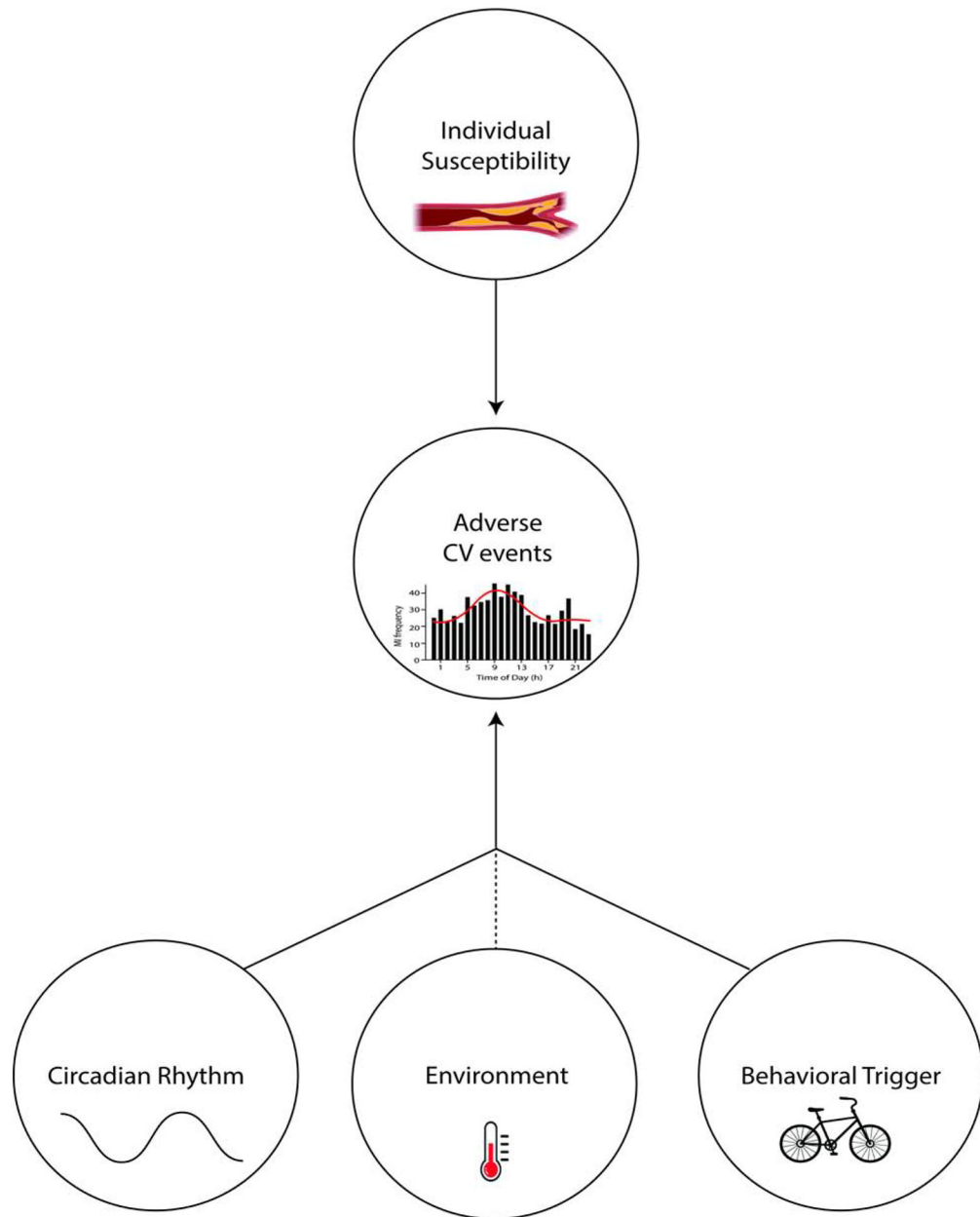
Figure 2. Interaction between individual susceptibility, circadian rhythms, behavioral triggers and environmental factors can increase the risk for adverse cardiovascular events.
In vulnerable individuals (e.g. people with atherosclerosis), a behavioral trigger (e.g. exercise) can interact with underlying circadian rhythms in resting CV variables (e.g. hemostatic system) and lead to an adverse CV event. This interaction can also be affected by environmental factors (e.g. exercising in extreme temperatures).