Sleep Medicine Reviews 16 (2012) 151–166

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Circadian rhythms and cardiovascular health

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ARTICLE INFO

Article history:
Received 3 March 2011
Accepted 27 April 2011
Available online 8 June 2011

Keywords:
Blood pressure
Hypertension
Myocardial ischemia
Acute myocardial infarction
Sudden cardiac death
Arrhythmias
Circadian rhythm
Chronobiology
Chronotherapy

SUMMARY

The functional organization of the cardiovascular system shows clear circadian rhythmicity. These and other circadian rhythms at all levels of organization are orchestrated by a central biological clock, the suprachiasmatic nuclei of the hypothalamus. Preservation of the normal circadian time structure from the level of the cardiomyocyte to the organ system appears to be essential for cardiovascular health and cardiovascular disease prevention. Myocardial ischemia, acute myocardial infarct, and sudden cardiac death are much greater in incidence than expected in the morning. Moreover, supraventricular and ventricular cardiac arrhythmias of various types show specific day-night patterns, with atrial arrhythmias – premature beats, tachycardias, atrial fibrillation, and flutter – generally being of higher frequency during the day than night – and ventricular fibrillation and ventricular premature beats more common, respectively, in the morning and during the daytime activity than sleep span. Furthermore, different circadian patterns of blood pressure are found in arterial hypertension, in relation to different cardiovascular morbidity and mortality risk. Such temporal patterns result from circadian periodicity in pathophysiological mechanisms that give rise to predictable-in-time differences in susceptibility-resistance to cyclic environmental stressors that trigger these clinical events. Circadian rhythms also may affect the pharmacokinetics and pharmacodynamics of cardiovascular and other medications. Knowledge of 24-h patterns in the risk of cardiac arrhythmias and cardiovascular disease morbidity and mortality plus circadian rhythm-dependencies of underlying pathophysiologic mechanisms suggests the requirement for preventive and therapeutic interventions is not the same throughout the day and night, and should be tailored accordingly to improve outcomes.

Introduction

Biological processes and functions oscillate rhythmically in time. Circadian rhythms, which are of particular relevance to everyday life and clinical medicine, are controlled by an inherited master clock residing in the paired suprachiasmatic nuclei (SCN) of the hypothalamus.[1] Rhythmic activities the SCN clock genes Per1, Per2, Per3, Bmal, Clock, and Cry and their gene products comprise the central time-keeping mechanism. Transcription factors CLOCK and BMAL1 drive the expression of Per1, Per2, Cry1, Cry2, plus a variety of clock-controlled genes, i.e., target genes that are not integral clock components and that do not feedback on CLOCK/BMAL1, via E-box sequences in their promoters. PER and CRY proteins negatively feedback on the transcriptional activity of CLOCK:BMAL1, which results in a circadian rhythm in expression of the CLOCK:BMAL1-driven clock and various clock-controlled genes. Precision of the period and staging of circadian rhythms is achieved via cyclic environmental time cues. The ambient light–dark cycle is the most important cue under normal conditions, with the retinohypothalamic neural projection relaying information sensed by specialized non-cone and non-rod receptors of the retina to the SCN about the timing of light onsets and offsets during each 24-h period. The biological time-keeping system also includes the multitude of peripheral cell, tissue, and organ circadian clocks that are regulated and coordinated by the master SCN clock. The output of the central and peripheral circadian clocks is mediated by various clock-controlled genes, giving rise to the body's circadian time structure (CTS) that is appropriately staged by environmental

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doi:10.1016/j.smrv.2011.04.003

Abbreviations

ABPM	ambulatory BP monitoring
ACEI	angiotensin-converting enzyme inhibitor
AF	atrial fibrillation
AMI	acute myocardial infarction
ANS	autonomic nervous system
ARB	angiotensin II receptor blocker
AV	atrio-ventricular
BP	blood pressure
CAD	coronary artery disease
CTS	circadian time structure
CVD	cardiovascular disease
DBP	diastolic blood pressure
ECG	electrocardiogram
FFI	fatal familial insomnia
HR	heart rate
HRV	heart rate variability
MI	myocardial ischemia
MSA	multiple system atrophy
nREM	non rapid eye movement
OSAS	obstructive sleep apnea syndrome
PAF	pure autonomic failure
PD	pharmacodynamics
PK	pharmacokinetics
PSVT	paroxysmal supraventricular tachycardia
REM	rapid eye movement
SBP	systolic blood pressure
SCD	sudden cardiac death
SCN	suprachiasmatic nuclei
SN	sinus node
SNS	sympathetic nervous system
VF	ventricular fibrillation
VPB	ventricular premature beat
VT	ventricular tachycardia

time cues to support optimal human metabolic and performance efficiency and capability during diurnal activity and repair and rejuvenation during nighttime rest/sleep.

Circadian clocks have been identified in nearly all mammalian cells investigated, including cardiomyocytes, fibroblasts, vascular smooth muscle cells, and endothelial cells.[2–6] Although 24-h rhythms in heart rate (HR), blood pressure (BP), and cardiac output are classically attributed to rhythms in neuroendocrine constituents, rhythms at the cellular level also play an important role.[7–9] The evidence for this comes from a series of different studies. Genetic manipulation of circadian clock components, such as CLOCK and BMAL1,[10] variations within a tandem repeat of the human clock gene Per3,[11] and genetic ablation of the circadian clock within endothelial or vascular smooth muscle cells,[12] either alter, markedly attenuate, or abolish HR and/or BP circadian rhythms. Furthermore, studies on the cardiomyocyte-specific clock mutant mouse model, in which the cardiomyocyte circadian clock is temporally locked to the commencement of the inactive/sleep phase, show the cardiomyocyte clock differentially regulates cardiac metabolism and contractile function during the 24 h.[13–16] Furthermore, rodent models reveal it directly modulates myocardial ischemia/reperfusion tolerance in a circadian rhythm-dependent manner.[14] Recent findings also implicate the disruption (desynchronization) of circadian clocks in the pathogenesis of cardiovascular disease (CVD).[8,17] Circadian clocks are altered in numerous animal models of increased CVD risk, including aging, diet-induced obesity, diabetes mellitus, hypertension- and pressure overload-induced hypertrophy, simulated shift work, and ischemia/reperfusion.[18–24] Circadian desynchrony of the organism from its environment, either in humans through rotating shift-work schedules or in rodent through light/dark cycle or genetic alteration, augments CVD development.[25–28] Furthermore, rodent studies show chronic desynchrony of the circadian clock results in enhancement of cardiac mass, cardiomyocyte size, and expressed hypertrophic markers, thereby suggesting it influences responsiveness to pro-hypertrophic stimuli.[29]

Beyond the cellular level, circadian rhythms of cardiovascular physiology and function are very well established[30]; moreover, clear circadian rhythmicity is found in pathophysiological mechanisms that underlie 24-h patterning of morbid and mortal CVD events. Moreover, the administration time, relative to the staging of involved circadian rhythms, of various classes of medications used to manage CVD risk may impact, sometimes quite dramatically, their pharmacokinetics (PK) and pharmacodynamics (PD).[31] This infers it is necessary to tailor preventive and therapeutic interventions to circadian rhythm determinants to optimize intended outcomes.[32]

Recognition of the importance of circadian rhythms in cardiovascular functions and their involvement in 24-h patterns of CVD conditions and events has lead to renewed scientific interest in chronobiology, i.e., the study of biological rhythms. Indeed, investigation of the temporal structure of the sources and mechanisms of cardiovascular rhythms is a necessary preliminary step in understanding their clinical implications, especially in regard to CVD risk and its control through therapeutic interventions. The main sources of the time-dependency of cardiovascular physiology and pathophysiology are cyclic variation in external stimuli and demands, especially physical and mental activity and stress, and endogenous circadian rhythms, even though it is often impossible to clearly separate the relative contribution of each. This article discusses the relevance of circadian rhythms to the prevention and management of CVD, focusing on the three major clinical entities of arterial hypertension, myocardial ischemia (MI), and cardiac arrhythmias. Published pathophysiologic, epidemiologic, and clinico-therapeutic evidence clearly establishes the importance of a chronobiologic approach, both to uncovering new insight into the maintenance of cardiovascular health and to improving the prognostic assessment and therapeutic management of CVD patients.

Circadian rhythms in arterial hypertension

Systolic (SBP) and diastolic (DBP) BP exhibit distinct, although different, 24-h patterning among patients. In so-called normal dippers, the sleep-time BP mean is reduced by 10–20% relative to the daytime mean.[33] During the daytime, typically two daytime peaks are manifested, the first more prominent one shortly after morning awakening and the second late in the afternoon or early evening, with a small mid-afternoon nadir. In healthy young adults, the immediate morning SBP rise amounts to about 20–25 mmHg, but in the elderly, who have less compliant and elastic arteries, it can be as great as 40–60 mmHg. Bed-bound subjects, whether normotensive[34] or hypertensive,[35] and those with fixed HR[36] also exhibit significant BP decline during sleep, it being more pronounced in women than men.[37]

Non-dipping (<10% BP decrease in sleep-time mean relative to daytime mean) and even rising (sleep-time BP mean > daytime mean) 24-h patterns are common in secondary hypertension, which is caused by a co-existing medical condition. Super-dipping BP

patterns (>20% decrease in sleep-time BP mean relative to daytime mean) may occur in persons with autonomic nervous system (ANS) dysfunction, those treated too aggressively with hypertension medications, particularly when ingested in the evening, or in those with 'white coat' (i.e., pseudo) hypertension, abnormally high BP only in the presence of medical personnel in clinical settings.[38] Blunted or reversed BP sleep-time decline has been reported in orthostatic ANS failure,[39] Shy-Drager syndrome,[40] vascular dementia,[41] Alzheimer-type dementia,[42] cerebral atrophy,[43] cerebrovascular disease,[44,45] ischemic arterial disease after carotid endoarterectomy,[46] neurogenic hypertension,[47] fatal familial insomnia (FFI),[48] diabetes,[49] catecholamine-producing tumors,[50,51] Cushing's syndrome,[52] exogenous glucocorticoid administration,[53] mineralocorticoid excess syndromes,[54] Addison's disease,[55] pseudohypoparathyroidism,[56] obstructive sleep apnea syndrome (OSAS),[57] normotensive and hypertensive asthma,[58] chronic renal failure,[59,60] severe hypertension,[61] salt-sensitive essential hypertension,[62] gestational hypertension,[63] toxemia of pregnancy,[64] essential hypertension with left ventricular hypertrophy,[65] renal, liver, or cardiac transplant[66–68] related to immunosuppressive treatment, congestive heart failure,[69,70] and recombinant human erythropoietin therapy.[71] Moreover, a circadian profile characterized by daytime hypertension and sleep-time hypotension has been described in hemodynamic brain infarction associated with prolonged blood–brain barrier disturbance,[72] the range of variation between daytime activity and nighttime sleep being significantly increased from expected.

The circadian HR pattern closely parallels that of SBP and DBP in normal conditions and shows strong genetic dependency in terms of the daytime mean, amplitude of variation, and peak time during the 24 h.[73] There is no doubt the circadian HR rhythm is intrinsic and driven by 24-h variation in ANS activity. However, in all hypertensive conditions that result in loss or reversal of normal nocturnal BP reduction, nocturnal bradycardia is at least partially preserved, indicating the modulating influences of the two variables are only partially coincident. Further support of this notion comes from study of rats made hypertensive by transgenic implantation of the mouse salivary gland renin gene (TGR(mRen-2)27)[74]; the HR and BP circadian rhythms persist but their phasing manifests in complete opposition.

Circadian changes in the pathophysiological mechanisms of arterial hypertension

The 24-h BP variation results primarily from the cyclic exogenous alteration of physical and mental activity, stress, among others, coupled with the sleep–wake cycle. However, endogenous neurohumoral and other circadian rhythms also play a role,[75] although it is impossible to clearly separate the relative influence of the former form the latter. For sure, the effects of physical and mental activity account for the predominant proportion of the day-night variation,[76] as demonstrated by studies of shift workers who show a close linkage between physical activity and BP even on the first 24 h of night work.[77,78]

Endogenous mechanisms of the 24-h BP pattern also are clearly influenced by genetic factors.[79,80] BP dipping is a heritable trait which can be mapped by linkage analysis, with genetic control of arterial stiffness being the likely mechanism.[79,80] The endogenous basis for the 24-h BP variation is also supported by studies showing lesioning of the SCN of laboratory rodents abolishes BP and HR circadian rhythms without affecting sleep–wake and motor activity cycles.[81,82] Rodents are nocturnally active animals, and their BP circadian rhythm is characterized by elevated nighttime and decreased daytime BP values. Thus, the relationship of BP level to activity level is underlined in both human beings and laboratory rodents.

Sleep-related alterations of circadian BP rhythms

Sleep is the most important and consistent source of circadian BP variation.[83] BP variation varies with sleep stage[84,85]; lowest BP levels occur during deepest sleep, i.e., stages 3 and 4, whereas relatively higher BP levels, although generally not as high as awake-state BP levels, occur during less deep sleep, i.e., stages 1 and 2 and REM sleep. Significant BP increase takes places in the morning in diurnally active persons. Deep (delta or slow-wave) sleep prevails during the first half of nighttime rest coincident with nocturnal BP decline. During the last half of nighttime sleep, REM-related and brief arousal-related episodes of BP and HR rises increase in frequency. This is the likely explanation of why intra-arterial data aligned to the time of waking show the morning BP rise commences prior to awakening; thus, its attribution solely to awakening seems highly implausible.[86] Wrist actigraphy, a tool commonly used in sleep studies, has helped identify two distinct patterns of morning BP rise: one defined by gradual rise commencing before awakening and common in young persons and the other defined by steep BP rise commencing after waking and common in elderly persons who show pronounced responses to mental stress.[87]

Important additional influences of sleep on BP may be exerted through variation in respiration. During sleep onset and light NREM sleep, breathing is regular and periodic with only sporadic central apneas, and BP and HR decline. Oscillations of 3–5 s and 20–30 s in breathing are synchronous with oscillations of cortical electroencephalographic activity, BP, HR, and oxygen saturation. During REM sleep, breathing and HR become irregular and central apneas or hypopneas of a few seconds occur sporadically, often in association with bursts of REM. Hypertensive BP spikes, as great as 30–40 mmHg from baseline, occur abruptly and continue for the duration of the REM episode. During sleep, alveolar ventilation decreases by 0.4–1.5 l/min, and pulmonary arterial pressure rises by 4–5 mmHg; nonetheless, these variables remain within the normal range. Changes in sensitivity and functioning of homeostatic mechanisms account for these oscillatory phenomena, which also occur with similar periodicity in other pathophysiologic states[88,89] or with sleep onset.[90] Respiratory instability associated with the transition from mixed neurogenic and metabolic control of breathing typical of wakefulness to the purely metabolic state typical of NREM sleep is the underlying cause of the periodic oscillations.[91]

The stage organization of sleep is also reflected in ANS function,[92] a well established driver of the circadian BP profile.[93–95] Sympathetic nervous system (SNS) activity during deep NREM sleep is lower than during wakefulness. However, it increases in REM sleep to the same, or greater, level seen in wakefulness. During NREM sleep, activity of the sympathoadrenal branch of the SNS decreases, probably due to entrainment of the sleep–wake cycle, whereas low activity of the noradrenergic branches seems to depend mainly on the assumption of horizontal body posture during sleep.[96] During REM sleep, concomitant reduction in coronary blood flow[97] and increased coronary spasm[98] can be demonstrated. Not surprisingly, therefore, REM sleep is associated with elevated MI risk among individuals with coronary artery disease (CAD) or vasospastic angina.[98,99] Thus, REM sleep constitutes a period of potential CVD risk due to dramatic phasic SNS, BP, and HR fluctuation.

Loss or reversal of the expected normal physiologic sleep-time BP decline may result from the large number of medical disorders that cause insomnia. Unfortunately, objective studies have not been performed in the majority of these conditions, even though polysomnographic data demonstrate sleep disturbances in CVD,[100,101] ANS failure,[40,102–105] rheumatoid arthritis possibly in relation to

corticosteroid therapy,[106,107] chronic renal failure,[108] hyperthyroidism,[109] Cushing's disease and exogenous glucocorticoid administration,[110–113] and FFI.[114,115] It is also of relevance that sleep disturbances may be induced by a variety of acute and chronic common medical conditions, e.g., allergic rhinitis (sleep-time exacerbation of nasal obstruction often accompanied by sleep-disordered breathing),[116,117] atopic dermatitis,[118,119] asthma (a nocturnal condition in 75% or so of suffers),[120,121] osteoarthritis (arthritic condition characterized by inflammation and pain that builds during daytime activity and being most severe at night),[122] chronic pain syndrome (lowest pain threshold overnight),[123] peptic ulcer disease and gastric-esophageal reflux disorder (most severe late evening and very early morning hours after midnight),[124] congestive heart failure (dyspnea and increased work of breathing worse overnight),[125] nocturnal polyuria,[126–128] and voluntary chronic sleep loss/deprivation.[129] If chronic, these medical conditions may result in persistent sleep-onset insomnia and/or disturbed and discontinuous sleep, the consequence being increased risk of higher than normal overnight BP level and potential nocturnal hypertension with associated elevated hazard of end-organ injury to blood vessels of the brain, eye, kidney, and heart. It is usually assumed that anxiety and discomfort are the major causes of poor sleep, sometimes leading to generalized stress from sleep disruption.[130–132] Three conditions, namely sleep-disordered breathing, ANS failure, and FFI, for which the relationships between sleep and BP have been extensively, though not completely investigated, deserve detailed discussion for the relationships they imply between cardiovascular physiology rhythmicity and CVD disease prevention and treatment.

Sleep-disordered breathing and circadian BP rhythms

Sleep-disordered breathing is characterized by snoring and sleep apnea of various severity.[133] An abnormal breathing event is defined as snoring (clear inspiratory noise over the trachea), apnea (complete cessation of airflow $\geq$10 s), or hypopnea ($\geq$50% decrease in airflow $>$10 s). The snoring and apnea/hypopnea indices, i.e., average number of respective events/hour of sleep, serves to quantify sleep-disordered breathing. By convention, a snoring index $\geq$10 defines the presence of snoring, and an apnea/hypopnea index $\geq$10 defines the presence of sleep apnea. By means of these criteria, nonapneic snoring can be differentiated from OSAS. It is in OSAS that major alterations of the circadian BP profile are found, with obliteration of the sleep-related BP reduction and increase in BP variability.[134]

Cardiovascular changes that accompany OSAS events are now well recognized. HR, systemic BP, and pulmonary arterial pressure initially decline with the onset of apnea but then rise acutely with its termination. As a result, not only is BP variability increased, but also average BP level.[134] Cardiovascular reflex studies[135] reveal in subjects at rest significantly higher HR and plasma levels of norepinephrine, higher response of BP to head-up tilting, and by the cold face test significantly less respiratory arrhythmia, lower baroreflex sensitivity index, and lower Valsalva ratio associated with enhanced HR decrease. These findings in OSAS patients suggest sympathetic overactivity associated with blunting of reflexes dependent on baroreceptor or pulmonary afferents and normal or greater than normal cardiac vagal efferent activity.

Half or more of all OSAS patients are hypertensive, not only during nighttime sleep span but also during daytime activity.[136,137] Conversely, several studies have found an approximately 30% prevalence of OSAS among patients with primary hypertension.[138,139] Several candidate mechanisms have been advanced to explain how snoring and OSAS lead to sustained daytime elevation of BP and ultimately daytime hypertension. These include direct effects of episodic hypoxemia and hypercapnia on chemoreceptors and SNS overactivity,[140] cardiovascular system modification (including fluid balance) in response to marked fluctuations in intrathoracic pressure during obstructed breathing,[141] generalized stress from sleep disruption (i.e., arousal effect),[130,132] genetic factors, and age. The relative contribution of each factor remains unknown, and the role of recurrent hypoxia is particularly controversial. Conceivably, concerted action of several factors, e.g., hypoxia, negative intrathoracic pressure, intermittent BP changes, sleep arousal, and metabolic or endocrine factors, possibly only in combination with a particular age and specific genetically-determined characteristics, could bring about hypertension.[142] Whatever the causal factors, the common mechanism shared by hypertension and OSAS is activation of the SNS,[132,135] which somehow becomes chronic or acts as an intermediary, changing hormonal balance or causing vascular remodeling.

Undiagnosed sleep-disordered breathing might play a role also in the genesis of BP pattern alteration of some, if not all, nondippers diagnosed as essential hypertensives. This is more likely for male patients, since in the adult population snoring and OSAS are of much higher prevalence among men than women.[143] In this regard, we previously documented by polysomnographic study of a representative population of male essential hypertensive nondippers the manifestation of blunted sleep-related BP decline and increased BP variability in 10 of 11 apneic snorers.[144] Hence, undiagnosed apneic snoring could play an important role in determining changes in the circadian BP profile toward non-dipping.

Autonomic failure and circadian BP rhythms

Altered BP level and 24-h patterning can result from ANS failure in the form of a "pure" autonomic failure (PAF) without other neurological signs, previously termed "idiopathic orthostatic hypotension",[145] or from neurodegenerative disease, i.e., multiple system atrophy (MSA). The term MSA, first used by Graham and Oppenheimer in 1969,[146] refers to a sporadic adult-onset neurodegenerative disease that had previously been described variously as striatonigral degeneration, olivopontocerebellar atrophy, or Shy-Drager syndrome according to the clinical predominance of parkinsonism, cerebellar signs, and ANS failure, respectively.[147–149] The clinical picture[150] of MSA patients with ANS failure is highly variable, at least at its onset; it may include parkinsonism poorly responsive to levodopa, cerebellar syndrome, progressive ANS failure (postural hypotension, defective sweating, constipation, and erectile dysfunction in men), or variable combination of these syndromes. The prognosis of MSA with ANS failure is usually determined by progression of neurologic features over the course of about 6 years. In contrast, the natural history of PAF is of a slow progression over some 10–15 years.

All ANS failure patients manifest severe symptomatic postural hypotension. Those with MSA and ANS failure exhibit normal norepinephrine plasma levels when resting in supine position and show no significant increase when subjected to orthostatic stress. PAF subjects differ by having very low plasma levels of norepinephrine when resting in supine position and also show no elevation when subjected to orthostatic stress.[134] Complete obliteration of the circadian BP pattern is found in PAF patients, while reversal of the normal circadian BP profile is found in MSA patients with ANS failure. However, MSA patients without ANS failure express a normal BP rhythm.[134] These observations are consistent with the notion that normal day–night BP variation depends on proper SNS functioning.

Sleep abnormalities, (e.g., sleep fragmentation with greater than normal sleep latency, altered muscle tone, and abnormal movements; decreases in REM and stage 3 and 4 sleep; REM sleep

behavior disorder) are common in MSA, irrespective of ANS failure. However, such sleep abnormalities are absent in PAF patients, suggesting sleep disruption is mainly the consequence of central nervous system lesions[134] and ANS failure can induce nocturnal BP dysregulation independently of sleep abnormalities.

FFI and circadian BP rhythms

FFI is a hereditary prion disease characterized by a mutation at codon 178 of the prion protein gene cosegregating with the methionine polymorphism at codon 129 of the mutated allele. FFI presents as disturbances of the wake–sleep cycle, dysautonomia, hypertension, and somatomotor manifestations of myoclonus, ataxia, dysarthria, and spasticity.[151] The cardinal feature of FFI, total and sustained disruption of the sleep–wake cycle, constitutes a unique, albeit dramatic, opportunity to observe how the chronic absence of sleep impacts human circadian rhythms. In FFI, dominant 24-h rhythmicity is detectable both in BP and HR.[48] However, as a combined result of its decreased amplitude and shifted phase, the nocturnal BP fall is lost early during disease evolution, even though nocturnal bradycardia is still preserved. A rhythmic BP component persists, although of lower amplitude and shifted phase, for months after the total cessation of the sleep–wake circadian rhythm. Only in its terminal stage is there complete obliteration of 24-h BP variation. In addition, no association with the pattern of motor activity or meals can be detected. These findings support the existence of an intrinsic component of the BP rhythm that is independent of the sleep–wake and rest–activity cycles.

Dysautonomia is an important feature in FFI; however, changes in pituitary–adrenal functioning also seem to contribute significantly to the pathogenesis of the hypertensive condition. In FFI, abnormal nocturnal peaks are detected in the circadian rhythm of plasma ACTH and cortisol concentration, commencing in its earliest stages, i.e., before development of hypertension and clinical and instrumental signs of severe dysautonomia.[48] It is of interest that nocturnal peaks of these hormones, similar to those found in FFI and representing reversal of the normal sleep-related inhibition of secretion, have been produced in healthy subjects by acute sleep deprivation.[152–154]

FFI changes occur not only in rhythms of the cardiovascular system and functions,[48] but also in neurohumoral rhythms,[155,156] indicating this prion disease disturbs and eventually obliterates the endogenous CTS. Although nothing can be drawn from our data regarding basic mechanisms underlying progressive obliteration of the CTS found in FFI, it is very tempting to hypothesize the prion protein plays a role in the origin and modulation of human circadian rhythms, analogous to the role of the per protein in Drosophila.[157] Recent demonstration that mice devoid of prion protein exhibit clear CTS alteration[157] further suggests it plays such a role. Hence, future research in this direction is warranted.

Prognostic and therapeutic implications

Physiological temporal balance with predominant circadian rhythmicity exists between the various neurohumoral factors integrating BP regulation.[158–160] Loss of this temporal balance may be a pathogenetic mechanism of hypertension and should be taken into account in its clinical management.[60,70,161,162] Moreover, it is bound to differentially affect the response of individuals to pharmacologic treatment and constitutes, in part, the basis for the chronotherapy of hypertension, i.e., delivery of medications in synchrony with biological rhythm determinants to enhance desired outcomes and/or minimize/avert adverse effects.[163] During the past two decades, specific features of the 24-h BP pattern, as determined by around-the-clock ambulatory BP monitoring (ABPM), have been assessed as potential sources of injury to target tissues and triggers of cardiac and cerebrovascular events. Thus, a growing number of studies[164–167] have consistently shown association between blunted sleep-time BP decline and increased incidence of fatal and nonfatal CVD events. Independent prospective studies and recent meta-analyses have also found the asleep BP mean to better predict CVD risk than the awake or 24-h BP means.[166,168–172] Most important, a recent prospective randomized trial involving hypertensive subjects systematically evaluated by periodic (at least annually) ABPM for over 5 years has documented the progressive decrease in asleep BP and increase in sleep-time relative BP decline toward the normal dipping pattern, two new novel therapeutic targets best achieved with bedtime hypertension therapy, to be the most significant predictors of CVD event-free survival.[173]

Appreciable ingestion-time differences in the PK – absorption, distribution, metabolism, and elimination – and PD – independent of PK phenomena – of BP-lowering medications are well known.[83,174] The former result not from meal effects or posture, but circadian rhythms in gastric pH and emptying, gastrointestinal motility, biliary function, hepatic enzyme activity, blood flow to the duodenum and other organs of the gastrointestinal tract, and glomerular filtration rate, among others.[175] Hence, one might expect antihypertensive medications to be cleared more slowly overnight, thereby potentially prolonging their duration of action when ingested at bedtime than upon morning awakening.[176] Administration-time differences in the PD of BP medications, in the absence of differences in PK, are also known[177]; they most likely result from circadian rhythms in circulating drug-free fraction, rate-limiting steps of key biochemical and metabolic processes, receptor number and conformation, and/or second messenger and signaling pathways.[178] A number of published clinical trials, reviewed in-depth elsewhere,[176,177,179] document a variety of highly prescribed calcium channel blocker, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), α-blocker, β-blocker, and diuretic medications when studied by around-the-clock ABPM methods display very significant, and sometimes dramatic, morning–evening dosing-time differences in BP-lowering effects. In particular, once-daily evening, in comparison to morning, scheduling of ARBs and ACEIs results in stronger therapeutic effect on asleep BP without loss of efficacy during the hours of diurnal activity. This administration-time effect is not dependent on the terminal half-life of the individual medications trialed, which ranges from 6 to 9 h for the ARB valsartan to ~40 h for the ACEI spirapril.[180,181]

The chronotherapeutic approach to hypertension is justified by the fact that BP is usually lowest at night as is sodium excretion. When sodium intake is excessive or its daytime excretion hampered, nocturnal BP is adjusted higher via the pressure/natriuresis mechanism to a level required for compensation overnight, the result being non-dipping 24-h BP patterning.[182] In diurnally active persons, the entire circadian BP pattern may be reset to a lower mean level and to a "more normal" day–night variation, simply by enhancing natriuresis nocturnally – the time-of-day when it can be most effective. A modification as simple and inexpensive as switching the ingestion time of one or more prescribed hypertension medications from morning to evening, may alone be sufficient to normalize nighttime BP, exerting an effect like that of sodium restriction.[183]

Twenty-four-hour pattern in MI

MI is the underlying pathogenetic mechanism of multiple clinical manifestations of CVD events: transient ischemic episodes, acute myocardial infarction (AMI), and sudden cardiac death (SCD).

MI may result from either restricted and insufficient oxygen supply or increased oxygen demand. A number of physiologic variables are crucial in determining mismatch between myocardial oxygen supply and demand, and predictable circadian changes are exhibited by all of them.[32] Such predictable-in-time differences in the susceptibility to MI, on the one hand, and in the pathogenetic mechanisms of MI, on the other hand, result in corresponding time-of-day differences in its overt expression and manifestations.

Twenty-four-hour pattern of transient MI events

Analysis of 24-h electrocardiogram (ECG) recordings of untreated diurnally active patients reveals episodes of transient ST-segment depression, including silent, i.e., non-symptomatic, MI are two-to-three-fold more frequent in the morning, between 06:00 h and noon, than at night.[184,185] A secondary vulnerability to transient ischemic episodes is sometimes observed later in the day, between 18:00 and 20:00 h.[186] The same circadian distribution is shown by symptomatic, i.e., chest-pain associated episodes of ST-segment elevations.[187] Moreover, greater ST-segment displacements are found when exercise is performed at 16:00 h than at 08:00 h,[188] indicating circadian rhythm-dependent difference in ischemic response of the myocardium to exercise. Finally, so-called variant angina, a form of MI that results from coronary artery vasospasm and expressed as ST-segment elevation, shows different circadian patterning, being most frequent during the second half of the nocturnal sleep span, between 02:00 and 04:00 h,[189] and more frequent during morning than afternoon exercise.[190]

Twenty-four-hour pattern of AMI

Published case series and population-based studies of temporal patterns in AMI have relied solely on the clock time of events. It is assumed such data are representative of events of at-risk individuals adhering to a common diurnal activity-nighttime sleep routine. However, since a significant proportion of the working population in Western countries is employed in night or rotating shift work, this assumption is invalid. Nonetheless, a great number of reports substantiate AMI onset is lowest during the first part of the night, increased during the second part of the night, and highest during the initial hours of diurnal activity, between 06:00 h and noon,[191,192] when the peak incidence rate of 40% (relative risk: 1.38) of the total episodes is observed.[192] The temporal relationship with awakening, rather than clock time, is verified by studies on shift workers with a reversed sleep–wake routine and also evening-types ('owls') with very late nocturnal bed and diurnal wakening times.[25,193] A different pattern in AMI onset defined only by a minor evening peak or absence of 24-h variation has been reported in cohorts of patients with history of smoking, diabetes,[194,195] CVD, stroke,[196] or previous other non-Q-wave type AMI,[195] congestive heart failure, or non-Q-wave type AMI.[194,195] Unfortunately, most studies have failed to take into account possible effects of differences in the sleep–wake routine of cases (in the United States about 15–20% of the work force is likely to be engaged in night or rotating shift work) and also scheduled medications. Prominence of the morning peak in AMI onset, despite the potential effects of these and other deterministic variables, suggests the actual morning risk of AMI may be underestimated.

Twenty-four-hour pattern of SCD

SCD, an extreme manifestation of MI, exhibits marked 24-h variability in occurrence, with prominent morning peak between 06:00 h and noon (when the incidence rate of SCD is 29%; relative risk: 1.29), secondary afternoon peak, and nighttime trough.[192,197]

Circadian changes in the pathophysiological mechanisms of MI

MI is thought to be triggered by several pathophysiological mechanisms, particularly the sudden morning increase of BP, HR, SNS activity, basal vascular tone, vasoconstrictive hormones, prothrombotic tendency, platelet aggregability, plasma viscosity, and hematocrit.[198] Each of these variables exhibits prominent circadian rhythmicity in phase with the reported 24-h pattern of the ischemic events.

Role of sleep

More than 80% of the episodes of ambulatory MI are associated with substantial increases in HR.[199,200] The relative tachycardia that accompanies morning arousal from sleep at night results in increased myocardial oxygen demand[199] and contributes to the excess morning frequency of MI, AMI, and SCD.[200,201] However, ischemic events occur also during sleep, especially in persons with severe CAD and vasospastic (variant) angina. As previously discussed, the strong circadian relationships between sleep, BP, and HR help explain why MI may be triggered overnight during REM sleep.[98,99] This risk is time-dependent, considering that episodes of REM sleep occur preferentially during the last half of the nocturnal rest span. Thus, the time-dependent early morning increase in MI risk appears to be determined, at least in part, by the circadian rhythm of REM sleep propensity through increased levels of "SNS activity", HR, and BP.

Role of neurohumoral factors

Other endogenous circadian rhythms are also involved in the elevated morning-time risk of MI. Plasma norepinephrine level[202,203] and plasma renin activity, which exhibit profound circadian variation and achieve peak levels in the morning,[204] induce coronary vasoconstriction.[205] A circadian rhythm in vascular basal tone is also demonstrated[206] in relation to increased morning α-sympathetic vasoconstrictor activity. In addition, ischemic threshold is lower at this time,[207] suggesting increased ischemia-induced coronary vascular resistance. This finding is further supported by the similar temporal variation in post-ischemic forearm vascular resistance.[207] Thus, the low morning ischemic threshold presumably mirrors the corresponding-in-time elevated coronary vascular resistance. In addition, the circadian pattern of plasma cortisol secretion, characterized in diurnally active persons by a sharp morning rise,[208] contributes to reduced coronary blood flow by increasing sensitivity of epicardial vessels to vasoconstrictor stimuli.[209]

Prognostic and therapeutic implications

Only limited data are available on the prognostic implications of the temporal variation in the inducing mechanisms of MI. However, it is known the (biological) time of AMI onset seems to affect its clinical course and outcome.[210] On average, AMIs that commence in the morning between 06:00 h and noon in presumably day-active persons are of greater infarct size than those that commence at other times of the day or night, whereas those that occur between noon and 06:00 h carry a significantly lower risk of circulatory arrests from ventricular arrhythmias than ones that commence at other times.[211] Moreover, the circadian time of AMI affects the success rate of thrombolysis; it is much poorer in patients who manifest an AMI in the morning than in those who manifest it at other times during the 24 h.[212]

All types of medications may show administration time (i.e., circadian rhythm)-dependent differences in their PK and/or PD[213]; however, medications used to treat MI patients are also bound to be influenced by the circadian staging of rhythms in underlying physiopathogenic mechanisms. It is noteworthy that a number of anti-ischemic medications show clinically significant ingestion-time differences in their PK and PD. A detailed review of all the temporal issues of antianginal medications is beyond the scope of the present paper, but can be found elsewhere.[214,215]

The 24-h rhythmic organization of cardiovascular functions is such that the defense mechanisms against MI are incapable of providing the same degree of protection throughout the day and night. Instead, temporal gates of excessive susceptibility exist, particularly in the morning and to a lesser extent in the evening, to aggressive ischemia-inducing mechanisms through which overt clinical manifestations may be triggered. Peak levels of critical physiologic variables, such as BP, HR, rate-pressure product (SBP × HR, surrogate measure of ventricular work and myocardial oxygen demand), SNS, and plasma concentrations of endogenous vasoconstricting substances, are aligned together at the same circadian time, in the morning in day-active persons, giving rise to heightened risk of ischemic events then. Thus, even relatively minor environmental stimuli that are usually harmless, like physical and mental stress, may precipitate AMI or SCD in the morning. Accordingly, the requirement for preventive and therapeutic interventions varies predictably during the 24 h. We feel that therapeutic strategies ought to be tailored to prevent the excessive risk of morning as well as late afternoon/evening AMI events. This implies the delivery of anti-ischemic medications, either alone or in combination, needs to be synchronized in time during the 24 h in proportion to predicted need, as documented by established rhythmic patterns in MI risk, and in a manner that will avert or minimize undesired side effects conventionally monitored in the clinic as well as those indicative of disruption of biological time-keeping systems. Thus far, only a few selected MI chronotherapies have been developed and approved by governmental agencies for marketing. The relative merit of these in comparison to conventional therapies in reducing ischemic events, especially in the morning when risk is greatest, and improving patient quality of life remains unresolved, since large prospective trials have yet to be conducted.[214]

Circadian rhythms in arrhythmias

Circadian variations have been established also in the pattern of presentation of both supraventricular[216,217] and ventricular cardiac arrhythmias,[218–220] irrespective of the presence or absence of concomitant medications.[221] In clinical practice, many arrhythmic episodes are observed as a consequence of MI, a pathophysiologic event that exhibits profound 24-h patterning, as previously related. However, the distribution during the 24 h of malignant arrhythmias is similar in patients with and without evidence of ischemic heart disease,[222] suggesting the importance of other factors.

Interpretation of data reported in the medical literature on circadian patterns in cardiac arrhythmias is complicated. This is because the conduct of previous studies were confounded, at least to some extent, by key factors extraneous to intrinsic arrhythmogenic activity that were overlooked by investigators, such as consumption of alcohol, caffeine, and other sympathomimetic substances, time and dose of prescription and perhaps illicit drugs, and differences in sleep–wake routine between subjects of various cohort studies. Because of these and other confounders, the findings of some studies may have been biased resulting in inappropriate conclusions. Moreover, the failure to recognize the capability of concomitant diseases, e.g., diabetes, renal failure, and heart failure, among others, to alter the circadian pattern of certain functional triggers of arrhythmias, like ANS activity and HR and BP, may also occasionally contribute to seemingly contradictory findings.

Circadian rhythms of atrial arrhythmias

Circadian patterning in atrial arrhythmias has been little studied, probably because of their relatively benign nature. Atrial arrhythmias – premature beats, tachycardias, atrial fibrillation (AF), and flutter – appear to exhibit circadian patterning, being of higher frequency during the day than night and with the abnormal atrial foci under the same long-term ANS regulation as normal pacemaker tissue.[223] A notable exception is AF. Paroxysmal AF is classified into two types according to onset time and ANS tone. Vagotonic ones typically occur at night, and adrenergic ones during the day.[224,225] Coumel et al.[224] found patients with vagally mediated AF tend to be younger, always have idiopathic AF, experience occurrences at night, and do not have a tendency toward persistent AF. In contrast, the adrenergically mediated type is opposite to the vagal type in all respects. Persistent AF, as studied with implanted atrial defibrillators, shows circadian distribution of onsets, i.e., predominant during the day.[225]

Pritchett et al.[226] documented paroxysmal supraventricular tachycardia (PSVT) by telephone transmission of the ECG of 14 apparently diurnally active patients treated with the calcium channel blocker medications of verapamil or diltiazem. Measuring the "tachycardia-free periods" between commencement of therapy and first recurrence of tachycardia as well as between successive recurrences, they found PSVT episodes were uniformly distributed during the span of wakefulness, between 09:00 h and midnight, whereas no tachycardia was noted between midnight and 09:00 h Moreover, the occurrence of PSVT was uniformly distributed throughout medication dosing intervals without predilection for tachycardia during the time of presumed plasma trough drug levels. However, different results were obtained for untreated diurnally active patients.[216] The PSVTs were atrio-ventricular (AV) nodal reentrant or AV reciprocating tachycardia types. Highest relative incidence of PSVT was at 16:00 h, when PSVT was five times more likely than at 04:00 h, the time of lowest relative incidence. If the relative incidence of attacks of PSVT is confirmed in future studies to be highest in the afternoon, one would expect targeting antiarrhythmic medications to this time of highest risk to improve therapeutic outcome.[216] In patients referred to an emergency department, Kupari et al.[227] observed two peaks in the frequency of PSVT onset, one in the morning between 06:00 h and noon and the other in the evening between 18:00 h and midnight. Neither the etiology of the arrhythmia nor preceding alcohol consumption appeared to modify this tendency, although administration of β-adrenergic blocking medication shifted the morning surge of arrhythmias to the nighttime, between midnight and 06:00 h.

Another study found symptomatic patients referred to a mobile coronary care unit[228] experienced greatest frequency of PSVT during the daytime and least frequency between midnight and 08:00 h. AF was also investigated in this study[228]; peak incidence occurred between midnight and 02:00 h, with secondary peaks in the morning between 08:00 and 09:00 h and afternoon between 14:00 and 16:00 h. Isolated AF, as well as AF associated with organic heart disease, exhibited the same 24-h pattern. Moreover, circadian fluctuation of the ventricular response to AF, when investigated by ambulatory Holter monitoring outside the hospital,[229] revealed prominent circadian patterning, with an early afternoon peak and nocturnal trough, likely due to increased vagal tone during sleep, which would be expected to increase AV node refractory period.

Several factors may contribute to the above-discussed differences between studies in the circadian pattern of PSVT. Different clinical settings (mobile vs. hospital coronary care unit, vs. emergency departments) and patients of different countries and cultures are bound to determine variable thresholds for seeking emergency care, which in turn becomes a selection bias in determining which arrhythmic episode will be recorded (if sufficiently symptomatic) and which will not (if relatively asymptomatic). Differences in treatment strategies, including class, dose, and schedule of medications, of treated cohorts and also the timing of sleep and wakefulness during the 24 h also are of major importance. Nonetheless, all the studies are consistent in reporting low incidence of PSVT during presumed nighttime sleep.

Circadian rhythms of AV block

A 24-h pattern, with morning preference, in the onset of symptomatic third-degree AV block was demonstrated in an emergency room setting,[230] similar to the one in SCD and cardiogenic cardiac arrest.[231] The etiology of this 24-h pattern is unknown; it may be an expression of intrinsic biological rhythmicity within cardiac tissue or its control system and/or the timing of environmental triggers culminating in coronary ischemia.

Circadian rhythms of ventricular premature beats (VPBs)

The frequency of VPBs, primarily based on studies conducted in patients affected by ischemic heart disease, appears to be decreased by as much as 50% during nighttime sleep relative to diurnal activity,[232,233] with the minimum number of events recorded between midnight and 02:00 h and greater number widely dispersed throughout the day, but without a clear peak time.

The morning increase in SCD as previously discussed might be related, at least in part, to increased frequency of ventricular arrhythmias, since highest prevalence (about one-third) of complex or frequent ventricular arrhythmias, as well as higher mean number of VPBs/hour, are observed between 06:00 h and noon.[234] In contrast with this conclusion are the findings of Goldstein et al.,[235] who did not find any relationship between the circadian rhythm of ventricular ectopic activity and cardiac mortality, prompting the conclusion the circadian rhythm in VPBs is not predictive of sudden death in patients with a high frequency of this type of arrhythmia.

The observed nocturnal decrease in VPBs was found to be reproducible, as established through replicate 24-h ECG monitoring studies.[233,236] Only two studies[237,238] reported no nocturnal decrease in VPBs; however, altered sleep patterns[238] or absence of circadian rhythmicity in ANS activity[237] may have contributed to these contrasting findings. Another study documented a nocturnal peak of VPBs in only one-half the patient sample, but these findings were probably affected by hypertrophic cardiomyopathy. Treatment for six-weeks with the β-blocker medication propranolol did not reduce the frequency of VPBs in recent AMI patients.[239] However, propranolol (60 or 80 mg three times a day (t.i.d.) was protective against the morning surge in VPBs associated in time with awakening from nocturnal sleep, with persistence of the therapeutic effect throughout the day.[239,240]

Circadian rhythms of ventricular tachyarrhythmias

Ventricular tachycardia (VT) and ventricular fibrillation (VF) show circadian variability in their occurrence. For example, Lucente et al.[241] demonstrated a significant circadian rhythm of VT based on Holter ECG tracings of AMI patients studied before antiarrhythmic treatment. A late-morning peak prevailed among patients who suffered an AMI in the distant past, while an afternoon peak in VT prevailed among patients who had an AMI recently. Unfortunately, patients with recent AMI were studied in the hospital whereas those with an earlier AMI were studied at home. Thus, difference in study conditions confounds the comparison of the respective patterns in VT between the two patient groups. In another study, Twidale et al.[242] studied the clock time of VT onset in 68 AMI patients. VT was not associated with AMI in 53 of them, as documented by 12-lead ECG. The remaining 15 patients, who did not have a previous medical history of sustained VT, had a medical history of syncope or presyncope of unknown etiology and experienced sustained monomorphic VT induced during electrophysiological study. In this patient subset, peak VT onset occurred between 10:00 h and noon.

Widespread use of implantable defibrillators set to automatically detect, record, and terminate episodes of VF facilitates study of their temporal patterns. Such derived data reveal a circadian pattern of VF, with primary morning peak between 07:00 and 11:00 h and much smaller secondary peak between 16:00 and 20:00 h.[220,243] This typical 24-h pattern characterized by major morning and secondary afternoon peaks was confirmed by Englund et al., who found it to be closely similar in both ischemic and non-ischemic heart disease patients, suggesting triggering mechanisms of VF may be similar and independent of underlying heart disease.[222]

Indirect confirmation of the daytime prevalence of ventricular tachyarrhythmias comes from a large cohort study demonstrating much greater proportion of cardiac arrests associated with VF or VT in public settings, assumingly the hours of daytime activity, than at home, assumingly the evening and nighttime.[244] Interestingly, cardiac arrest survival was much greater (odds ratio: 2.49) for those VF and VT events that occurred in public settings, i.e., daytime, than at home, i.e., evening and nighttime, findings consistent with ones of an experimental murine model demonstrating ischemic damage consequent to cardiac arrest is much worse when occurring during the rest than active phase of the 24 h.[245]

Fries et al. compared the circadian pattern of VF with that of the parameters derived from the spectral analysis of HR variability (HRV), a marker of ANS activity, in recipients of implantable cardioverter-defibrillators.[246] Twenty consecutive recipients were studied, comparing the circadian rhythms of HRV in patients with and without the typical morning peak of VF. The HRV marker of vagal activity displayed physiological circadian variability, i.e., highest values during nighttime sleep, only in patients without the morning peak of VF, and inverse circadian variability, i.e., lowest values during sleep, in patients showing the clear morning peak in tachyarrhythmias. As pronounced adrenergic hyperactivity in heart failure is the probable explanation for the paradoxically reversed HRV circadian pattern, the morning peak frequency of CVD events may be interpreted as a sign of cardiovascular overload caused by the natural change from sleep to activity upon awakening.

Circadian changes in the pathophysiological mechanisms of arrhythmias

Many functional, e.g., neurohumoral, electrolytic, hemodynamic, metabolic, etc., factors, aside from MI, may trigger and maintain arrhythmic episodes. Mechanisms by which these factors interact to determine an arrhythmogenic stimulus remain incompletely understood, constituting a major problem not only for the characterization of the determinants of the 24-h pattern of arrhythmias, but also for devising optimal conventional or chronotherapeutic and chronopreventive strategies. Arrhythmias are diagnosed by ECG, and it is of interest that many of ECG indices display significant circadian changes. In healthy subjects, P wave duration and its area, P–R interval, QRS duration, and QT interval

each shows circadian variation with the peak-to-trough difference equal to about 20% of the respective 24-h mean.[247–250] During the daytime, when SNS output is enhanced and HR increased, these indices are decreased, such that in diurnally active persons minimal values are expected between 10:00 h and 14:00 h.[247–250] During the night, following sympathetic withdrawal and parasympathetic dominance, these indices increase, attaining peak values between midnight and 06:00 h. These inherent changes during the 24 h, both in electrical activities and mechanical function, enable the heart to optimally meet workload demands during the daytime and favor or reflect repair and rejuvenation during overnight rest.

Circadian rhythms in electrical properties of the myocardium

Not only atrial, but also ventricular, rates exhibit circadian rhythmicity, with daytime peaks and nighttime troughs.[251,252] Circadian rhythmicity is also demonstrated in sinus node (SN) function, AV nodal and myocardial refractoriness, QT interval duration, and R and T wave voltage.[247,253,254] Temporal changes in SN function, with coefficients of variation over the 24 h as great as 10%, follow the ANS circadian rhythm.[254] SN recovery time, main index of SN function, is circadian rhythmic, with slowest recovery time between midnight and 07:00 h. The QT interval also exhibits similar variation, with longer QT interval during sleep than waking.[247,255] Moreover, the dispersion of the QT intervals (defined as the inter-lead QT variability in a 12-lead ECG), a simple method of evaluating repolarization heterogenicity of the ventricular myocardium, is greater during diurnal activity than nocturnal sleep,[256] both in CAD and non-CAD subjects.[257] In contrast, Manolis et al.[258] found a circadian rhythm of QT dispersion in heart failure patients, but with values higher during the night than the day; although, no such day–night difference was detected in subjects free of organic heart disease.

Ventricular refractoriness, i.e., duration of time required by ventricular fibers to recover excitability after depolarization, more directly reflects myocardial repolarization. Ventricular refractoriness is shorter during diurnal activity than nocturnal sleep.[255,259] In one study,[259] the ventricular refractory period was shortest around morning awakening, i.e., when SCD risk is highest.[260] Thus, circadian changes in the electrophysiological properties of the myocardium may play a very significant role in the complex pathogenesis both of arrhythmia initiation and SCD.

The circadian influence on refractoriness of normal cardiac tissues and accessory pathways exerts nocturnal protection against electrical induction of reciprocating tachycardia, but facilitates transient arrhythmia in the evening. In fact, there is 24-h variation in the frequency and pattern of ventricular arrhythmias, with significant reduction during sleep and absence during physical activity.[261] In patients with left-sided Kent bundles, i.e., bypass fibers between the atrium and ventricle thereby constituting an accessory pathway outside the normal conduction system and typical of Wolff–Parkinson–White syndrome, nocturnal protection against electrical induction of reciprocating tachycardia is associated with prolongation of atrial, AV nodal, ventricular, and Kent bundle refractoriness.[262] A greater number of VPBs are induced by hypoglycemia during daytime wakefulness than nighttime sleep.[263] HR[264] and left ventricular function[265] are major determinants of 24-h variation in the frequency of ventricular premature depolarization in subsets of patients; only those with premature beats of the HR-dependent type or those with left ventricular ejection fraction >30% show circadian rhythmicity. A circadian periodicity is demonstrated also in bradyarrhythmias[266] and ventricular response to AF.[229]

T-wave alternans, an integral component of congenital long QT syndrome, is a phenomenon of beat-to-beat variability in T-wave amplitude, morphology, and sometimes polarity that can trigger life-threatening ventricular arrhythmias. Based on a single report, this phenomenon too shows circadian variation, with highest occurrence (216 out of 320 episodes) between 07:00 h and 13:00 h. in presumably diurnally active persons.[267]

The possible influence of the circadian BP rhythm on arrhythmias has been studied, but with unclear results. A strong correlation between the incidence of VPBs and BP and HR was found in patients with left ventricular hypertrophy, while in the absence of hypertrophy supraventricular premature beats also exhibited higher incidence during peaks of BP and HR.[268] In another study, an independent positive correlation between BP and VPBs was found in 8 of 12 study subjects, while the HR was a negative, although nonsignificant, factor for ectopic beats.[269]

Altogether, the findings of the various studies suggest a primary role for neural activity in modulating the electrical disturbances underlying ventricular ectopy, even though at least one study reported no significant circadian variation in any electrophysiologic measure of ventricular electrical instability.[270] A contribution of other hormonal factors, especially adrenocortical ones, cannot be excluded.

Role of sleep on the electrical properties of the myocardium and arrhythmias

Bradyarrhythmias, particularly sinus bradycardia and AV blocks, are common during sleep.[271] Indeed, sinus pauses, second degree AV block, and greater frequency of PVBs and VT have been reported in OSAS[271–273] and obstructive lung disease.[274] They appear to be associated with hypoxia and can be eliminated by oxygenation, as demonstrated in the rat,[275] being more resistant to systemic hypoxia and reoxygenation during the activity than rest span, which is the only time when systemic hypoxia is proarrhythmogenic.[275] During sleep, PVBs appear to significantly decline in number, whereas premature atrial contractions are sometimes found to be increased.[232] The sleep-time reduction in PVBs correlates more closely with nocturnal HR than arousal level decline. Changes that occur during sleep can be explained by changes in autonomic mediation, with the sympathetic limb of the ANS exerting greater effect than the vagal limb.[276] Sleep appears to be protective against arrhythmias, regardless of when it occurs, since HR and BP are decreased even during an afternoon nap or siesta.[277] As expected, loss of ANS circadian rhythmicity, e.g., as observed in AMI patients,[237] is reflected by absence of nocturnal decrease in VPBs, confirming again the protective role of sleep and its associated physiology against arrhythmias.

In AF patients, the frequency of ventricular response is significantly lower during the night than day, implying the AV node refractory period duration is longer and AV conduction faster nocturnally.[278,279] In diurnally active persons, lowest ventricular response generally occurs between 03:00 and 05:00 h, and greatest ventricular response generally occurs between 22:00 h and midnight, a pattern consistent with circadian activities of the ANS.

Significant nocturnal prolongation of SN rate and recovery time, QT interval, and effective refractory period of the atria, AV node, and right ventricle has been demonstrated electrophysiologically. AV nodal and myocardial refractoriness follow a circadian rhythm, the peak being between 23:00 h and 08:00 h.[253] Moreover, shorter refractory periods during the day than night[280] may promote initiation of reentrant circuits within the myocardium, facilitating AF, and VF in high-risk patients. This mechanism may also explain why β-blocker therapy interacts with the circadian variation of electrophysiological properties of the myocardium,[259] possibly leading to suppression of the morning peak of malignant arrhythmias[281,282] and protection against SCD.[283]

The pacing threshold for ventricular capture increases by 5% during the nighttime relative to daytime.[284] In nocturnally active laboratory rodents, the electrical stability of the heart, as reflected by the threshold for VF induction by programmed electrical stimulation, is greatest during the first half of the activity span, with the total peak-to-trough circadian variation in VF threshold amounting to 25%.[285] A circadian rhythm in the threshold of malignant ventricular arrhythmias may contribute to some extent to the unequal distribution of SCD during the 24 h. In this regard, Venditti et al.,[286] in a review of recordings from implantable cardioverter-defibrillators, found a morning peak in defibrillation threshold and corresponding morning peak in failed first shock frequency. These findings suggest cardiac electrical instability is increased in the morning, thus facilitating VF induction and impeding VF termination.[285,286] An opposite pattern, with a morning nadir, was observed in the threshold of atrial defibrillation,[287] suggesting different regulatory electrophysiological mechanisms in AF versus VF.

Role of neurohumoral factors in cardiac arrhythmias

Fluctuations in ANS activity constitute major triggers of cardiac arrhythmias.[288] In addition to circadian rhythms in ANS activity, as discussed in previous sections, both norepinephrine and epinephrine plasma concentrations peak in the morning, around the time when diurnal activity commences, and are lowest during nighttime sleep.[289,290] A strong relationship exists between the circadian changes in plasma dopamine and norepinephrine and epinephrine, thus indicating dopaminergic modulation of circadian variation in SNS activity.[291] Increased SNS activity accelerates HR, favors spontaneous cardiac tissue depolarization, shortens ventricular effective refractory period, and decreases VF threshold.[271] In contrast, increased parasympathetic activity slows HR, decreases AV nodal conduction, and, in the presence of baseline SNS activity, increases both ventricular refractory period and VF threshold.[292] Spontaneous episodes of VT are often preceded by changes in HRV,[293] a reliable index of ANS activity.[294,295]

Nocturnal HR decline is an important physiological phenomenon. In monkeys, prevention by atrial pacing of the normal nocturnal HR decline results in rapidly progressing heart failure due to sustained elevated left ventricular workload.[296] This suggests alteration of normal nocturnal bradycardia should be regarded as an undesirable adverse effect of pharmacotherapy. However, no clinical data are yet available on the prognostic and therapeutic implications of such attributes of the HR circadian rhythm. β-Blockade eliminates the 24-h rhythm in ventricular refractory period, even though there is no clear relationship between ventricular refractoriness and plasma catecholamine levels.[259] This infers the day–night oscillation in SNS activity (which does not directly correlate with plasma norepinephrine concentrations) may be responsible for these observations. Circadian variation is found also in the atrial and ventricular refractory periods, with longer refractory periods during nighttime sleep than daytime activity.[280] Moreover, a clear relationship exists between ANS tone and circadian variation of refractory period.[280] Atrial and ventricular refractory periods are shorter when sympathetic tone is high, i.e., during the day, and are substantially lengthened when parasympathetic tone is high, i.e., during the night. Thus, the higher the sympathetic or parasympathetic activity of the ANS, the shorter or longer, respectively, is the refractory period. This relationship is also expressed as a strong negative correlation between atrial and ventricular refractory periods and ratio of the spectral power of the low and high frequency band (LF/HF) of HRV used as a measure of sympathovagal balance. In patients without structural heart disease, ANS activity (determined by HRV spectral analysis) significantly influences the time of AF onset. Both vagal and sympathetic activity increase immediately prior to AF onset in patients experiencing nocturnal episodes; however, vagal tone is more dominant, as shown by increase of the HF and LF components in the absence of significant variation in LF/HF ratio. Conversely, sympathetic tone increases immediately before AF in daytime-onset episodes.[297,298]

Prognostic and therapeutic implications of circadian rhythmicity in cardiac arrhythmias

Knowledge of circadian rhythms in cardiac arrhythmias and findings of tests used to determine their triggering thresholds are important, both for the optimal design of drug-delivery formulations and their accurate assessment. Evaluation of new dosage forms could be confounded by choice of an inappropriate biological time to conduct preclinical patient trials. Arrhythmogenesis appears to be suppressed during nighttime sleep, a phenomenon which is bound to influence results of studies done to assess efficacy of antiarrhythmic medications in relation to their administration time. Even defibrillator energy requirements of cardiac patients show circadian variation, supporting the potential merit of a chronotherapeutic approach to cardiac arrhythmias prevention. Since several types of common cardiac arrhythmias manifest predictable-in-time patterns, a chronotherapeutic approach to their prevention and treatment seems warranted.[299] Antiarrhythmic therapy tailored to be more intense during the hours of elevated risk signified by the peak frequency of arrhythmias seems promising. Yet, the advantage, i.e., increased drug efficacy and safety, of such a chronotherapeutic versus conventional (which aims at achieving constancy in drug concentration) approach, remains to be explored. We know of no studies that have been undertaken to assess the differential timing of antiarrhythmic drug administration as a means to improve therapeutic outcomes and increase patient tolerance. As a minimum, existing conventional formulations ought to be investigated for ingestion-time differences in antiarrhythmic efficacy. Up to now, relatively few conventional once-a-day anti-ischemic and anti-hypertensive medications – oral nitrates, calcium channel blockers, and α-adrenoceptor and β-adrenoceptor antagonists – have been compared for their differential effect and safety when administered in the morning versus evening.[214,300] Some of these medications may be considered antiarrhythmic in as much as they can prevent arrhythmias induced by MI episodes and/or HR and BP surges. Further research is warranted with more specific and potent antiarrhythmic preparations as a means of improving clinical management of cardiac arrhythmias and quality of life of at-risk patients.

Perspectives and conclusions

The purpose of this review has been to highlight the (chrono) epidemiology and chronobiology of CVD and potential underlying pathogenic mechanisms. Clinically significant 24-h patterns in hypertensive BP levels, MI, AMI, SCD, and various atrial and ventricular arrhythmias are known, having been established by clinical case series and population-based studies plus meta-analysis of the data of individual reports. Clinical epidemiologists initially emphasized environmental factors as triggers of the morning-time excess in MI, AMI, and SCD, primarily the abrupt change from nocturnal rest and inactivity to extensive morning physical exertion and mental stress, in coincidence with less than optimal coverage by preventive therapy due to end of dosing-interval drug trough levels. Initial chronobiology studies identified several key circadian rhythms, e.g., in HR, BP, SNS, basal

vascular tone, vasoconstrictive hormones, prothrombotic tendency, platelet aggregability, plasma viscosity, and hematocrit, the phasing of which is hypothesized to result in elevated vulnerability to CVD events at the commencement of diurnal activity.[198] The physiology and neuroendocrinology of sleep also plays a role in the pathogenesis and triggering of hypertensive target-organ damage, MI and CVD events, and in certain patients, especially hypertensive ones, risk of MI and CVD events is increased also nocturnally. A recent area of research involves the circadian clock of cardiomyocytes and its role in CVD pathogenesis. Of interest are the findings on rodent models implicating the importance of the circadian clock of cardiomyocytes in the differential regulation during the 24 h of cardiac metabolism, contractile function, and ischemia/reperfusion tolerance, suggesting its role in the pathogenesis of ischemic heart disease and cardiac arrhythmias. Rodent models further suggest disruption (desynchronization) of this circadian clock gives rise to cardiovascular dysfunction, which seemingly helps explain why rotating and night shift workers, in comparison to day shift workers, are at greater risk of developing CVD.

The prominent time patterns in CVD events necessitate new approaches to the clinical management of at-risk patients. It is taken for granted that clinical cuff BP measures are sufficiently representative, apart from those prone to 'white coat' or 'pseudo' hypertension. However, this is not the case. The literature is convincing that the sleep-time BP mean and nature of the 24-h BP pattern i.e., dipping vs. non-dipping, better predict the risk of cardiac and other target injury – as well as immediate (5-year) CVD morbidity and mortality – than daytime cuff values. In the realm of diagnostic medicine, ambulatory 24-h ECG monitoring is clinically accepted as a standard method to properly assess MI and cardiac arrhythmias, because they cannot always be captured during daytime inpatient clinical ECG evaluation. Similarly, 24-h ABPM is justified, in spite of the fact it is not currently recommended or financially supported by health maintenance and preventive medicine programs, because representative diurnal and nocturnal SBP and DBP values and 24-h patterning cannot be captured during a single very brief patient–doctor daytime encounter in the clinic. In the realm of therapeutics, almost all prescribed preventive and curative MI, hypertension, and cardiac arrhythmia therapies are formulated and scheduled to achieve constant or near-constant 24-h blood and tissue concentrations, even though each one of these conditions, some of which are potentially life threatening, show rather high-amplitude, predictable-in-time 24-h patterning of risk. Indeed, it seems counter-intuitive to strive for constancy of anti-ischemic and antiarrhythmic medication levels when the data overwhelmingly support the notion therapeutic strategies ought to be systemically varied during the 24 h in synchrony with biological need, which in the case of MI and certain arrhythmias is greatest in the morning. The advantage of hypertension chronotherapy has recently been substantiated by the 5-year outcomes MAPEC trial; reestablishing the circadian BP pattern, i.e., normal dipping, by scheduling one or more hypertension medications at bedtime, rather than scheduling them all in the morning, was associated with significant reduction in CVD events. Nonetheless, extensive review of the medical literature reveals a disappointing paucity of CVD chronotherapeutic initiatives, despite the promise such an approach may result in better individualization of treatment, improved drug efficacy, better patient tolerance, and hence better therapeutic compliance. Indeed, only a few selected so-called CVD chronotherapies have been developed and approved for marketing, and their relative merit versus conventional therapies is unverified, since prospective outcome trials have yet to be conducted. Future chronobiologic developments hopefully will involve greater understanding of the role circadian phenomena play at all levels of biological organization, especially at the cellular and molecular clock levels in CVD pathogenesis and event triggering and new circadian rhythm-based interventions to improve the clinical management and quality of life of at-risk patients.

Practice points

- Most patients show significant variation in SBP and DBP during the 24 h, with different 24-h patterns exhibited by different patients.
- ABPM devices are needed to properly assess BP levels throughout the 24 h to make an accurate diagnosis of hypertension as well as to evaluate the attainment of treatment goals.
- The sleep-time mean BP level and the extent of the sleep-time mean BP decline relative to the daytime mean level are sensitive predictors of CVD risk and thus worthy therapeutic targets.
- The 24-h pattern in MI arises from circadian rhythms in underlying pathophysiologic mechanisms and coincident time-of-day cyclic variations in environmental stressors.
- In many patients, the manifestation of supraventricular (atrial arrhythmias, PSVT) and ventricular (VPBs, VT and VF) cardiac arrhythmias exhibits significant circadian rhythmicity.
- The ingestion time (with reference to the CTS) of BP and heart medications can be a significant determinant of the magnitude of their beneficial effects and also patient tolerance.

Research agenda

- Explore the role of the cardiomyocyte circadian clock in cardiac tissue pathology.
- Knowledge of circadian rhythms in cardiac arrhythmias and MI should be used to better design improved drug-delivery formulations and to explore the advantage of a chronotherapeutic approach.
- Future research of 24-h patterns in supraventricular and ventricular cardiac arrhythmias must control for key factors extraneous to intrinsic arrhythmogenic activity, such as consumption of alcohol, caffeine and other sympathomimetic substances, time and dose of prescription medication, plus differences between subjects in sleep–wake routine which affect the phasing of involved endogenous circadian rhythm.

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