



Published in final edited form as:

Circ Arrhythm Electrophysiol. 2021 November ; 14(11): e010190. doi:10.1161/CIRCEP.121.010190.

Understanding Circadian Mechanisms of Sudden Cardiac Death: A Report From the National Heart, Lung, and Blood Institute Workshop, Part 2: Population and Clinical Considerations

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Declaration of Interest

F.A.J.L.S. has received lecture fees from Bayer HealthCare (2016), Sentara HealthCare (2017), Philips (2017), Vanda Pharmaceuticals (2018), and Pfizer Pharmaceuticals (2018).

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Abstract

Sudden cardiac death (SCD) is the sudden, unexpected death due to abrupt loss of heart function secondary to cardiovascular disease. In certain populations living with cardiovascular disease, SCD follows a distinct 24-hour pattern in occurrence, suggesting day/night rhythms in behavior, the environment, and/or endogenous circadian rhythms result in daily spans of increased vulnerability. The National Heart, Lung, and Blood Institute convened a workshop, “Understanding Circadian Mechanisms of Sudden Cardiac Death” to identify fundamental questions regarding the role of the circadian rhythms in SCD. Part 2 summarizes research gaps and opportunities in the areas of population and clinical research identified in the workshop. Established research supports a complex interaction between circadian rhythms and physiological responses that increase the risk for SCD. Moreover, these physiological responses themselves are influenced by a number of biological variables, including the type of cardiovascular disease, sex, age and genetics, as well as environmental factors. The emergence of new non-invasive biotechnological tools that continuously measure key cardiovascular variables, as well as the identification of biomarkers to assess circadian rhythms, hold promise for generating large-scale human datasets that will delineate which subsets of individuals are most vulnerable to SCD. Additionally, these data will improve our understanding of how people who suffer from circadian disruptions develop cardiovascular diseases that increase the risk for SCD. Emerging strategies to identify new biomarkers that can quantify circadian health (e.g., environmental, behavioral, and internal misalignment) may lead to new interventions and therapeutic targets to prevent the progression of cardiovascular diseases that cause SCD.

Keywords

cardiovascular diseases; circadian clock; circadian rhythm; genetics; National Heart; Lung; Blood Institute; population; sudden cardiac death

Introduction

The National Heart, Lung, and Blood Institute (NHLBI) convened a workshop, “*Understanding Circadian Mechanisms of Sudden Cardiac Death*,” in June 2019 that included experts in basic, translational, and clinical research in cardiovascular and sleep disorders, circadian biology and neuroscience. The participants represented academic institutions, as well as federal and non-federal agencies, and they were charged with identifying high priority gaps in population and clinical research, as well as future

opportunities for delineating circadian mechanisms contributing to sudden cardiac death (SCD).

Objectives:

1. Identify knowledge gaps that build on understanding the epidemiology of day/night rhythms in SCD occurrence, quantifying circadian health, and determining how circadian disruption impacts cardiovascular diseases that increase risk for SCD.
2. Determine which research findings are ready to be integrated into clinical research to develop strategies that mitigate SCD risk.
3. Identify chronobiological biomarkers and measurements that are particularly effective for assessing the risk of developing cardiovascular disease and SCD.

As the name implies, SCD is classically defined as the sudden, unexpected death due to abrupt loss of heart function. It is generally caused by underlying acquired or genetic cardiovascular disease, and sometimes, but not always, confirmed by postmortem examinations.^{1, 2} Despite the resources dedicated to addressing the underlying mechanisms, SCD continues to be a major public health problem, striking infants, children, young and older adults, and causing more than 300,000 deaths annually in the United States alone.

The risk for ventricular arrhythmias and SCD varies across the 24 hour period in certain populations living with cardiovascular disease (Figure 1).³⁻¹⁰ A common 24-hour pattern in SCD, as reported in the Framingham Heart Study³ and later reproduced in large prospective community studies, is a nighttime nadir followed by a morning peak in individuals that adhere to a routine of daytime wakefulness and nighttime sleep/rest.^{11, 12} These earlier studies found that the morning peak in SCD is associated with increased platelet aggregability and an increased frequency of myocardial infarction. More recent studies confirm the nighttime nadir but fail to demonstrate a morning peak.^{13, 14} There are several possible explanations for this discrepancy, including changes in: the primary causes of SCD, the number of people living with severe/advanced cardiovascular disease, identification of new populations living with cardiovascular disease, pharmacotherapies used to treat disease, and peoples' lifestyles. We now appreciate that different types of cardiovascular disease can result in distinct 24-hour patterns in the risk of SCD or arrhythmogenic events. The difference in patterns is particularly evident in people living with genetic syndromes, who show not only syndrome-specific but gene-specific differences in the 24-hour patterns of life-threatening events.^{8, 9} For example, people living with Brugada syndrome (BrS) show a peak incidence in ventricular fibrillation between midnight and 6 AM; people living with long QT syndrome type 1 show a peak incidence in ventricular events between noon and 6 PM; and people with long QT syndrome type 2 show a peak incidence in ventricular events between 6 AM and noon. Understanding the mechanisms as to why different patient populations show distinct patterns in the incidence of events at different times of day may lead to a better therapeutic strategy that improve clinical outcomes.

The existence of 24-hour patterns in the incidence of SCD in people living with cardiovascular disease suggest day/night rhythms in behaviors, ambient environment, and/or

endogenous circadian rhythms (Table) increase the risk of deadly events at specific times.¹⁵ Unmasking the circadian contribution from behavioral and/or environmental factors might enable clinician scientists to target each of these separately, thereby leading to the identification of novel chronotherapeutic and chronopreventive strategies (Table) that mitigate the risk of SCD and save lives.⁵

Circadian rhythms are intrinsic physiological rhythms with a periodicity of ~24 hours that prepare the body for predictable changes in the environment and activity.^{16, 17} For example, in diurnally active people, circulating cortisol levels rise during the last part of the night in advance of the demands on the circulatory and metabolic systems related to the abrupt increases in activity and energy expenditure that occur soon after awakening. These circadian rhythms are generated by cell autonomous circadian clocks, present in every nucleated cell in the body, that resonate with a periodicity of ~24 hours.¹⁸ Although ubiquitous, clock systems are organized hierarchically with a specialized role for the neurons in the central pacemaker, the suprachiasmatic nucleus (SCN) in the hypothalamus, identified as the control center that synchronizes the circadian rhythms in all the other tissues and systems throughout the body (Figure 2). Thus, the SCN regulates daily rhythms in physiology and behavior and changes its timing in response to direct retinal input to the SCN from intrinsically light-sensitive retinal ganglion cells.^{16, 17} This system enables the body to entrain (Table) to changing external light-dark cycles across annual seasons, after rapid travel to different time zones, or with exposures to artificial light.¹⁹

Lifestyles or diseases associated with circadian rhythm disruption (Table), including night shift work, diabetes mellitus, and obesity, are established cardiovascular disease risk factors. Furthermore, human studies in which the role of the endogenous circadian system is separated from the influence of the sleep/wake cycle has revealed endogenous circadian rhythms of many cardiovascular disease risk factors. These risk factors include blood pressure, inflammatory markers, platelet function, thrombogenic factors, and autonomic nervous system function. There is a growing body of evidence that circadian disruption can increase the burden or severity of some of these risk factors.^{20–28} Additionally, evidence shows a strong relationship between sleep disorders, such as obstructive sleep apnea (associated with severe sleep and wake-time autonomic imbalance, elevated sleep-time blood pressure, heart rate, and ventricular workload), and risk of cardiac arrhythmias, which may further heighten SCD susceptibility in those with past acute myocardial infarction, existing heart failure, and congenital heart disease.^{8, 9} Although we have made strides in understanding the extent of circadian control over cardiovascular physiology in healthy individuals, a lack of understanding of circadian pathophysiology is a major limiting factor impeding development of effective therapeutic strategies for preventing SCD caused by underlying cardiovascular diseases.

Gap 1: There is uncertainty regarding how circadian rhythms confer risk for sudden cardiac death and how to explain evolving epidemiology of day/night rhythm in the incidence of sudden cardiac death.

Opportunity: Determine how innate circadian rhythms interact with and modify the physiological responses to extrinsic arrhythmia triggers to create

time of day vulnerability to sudden cardiac death.—Many key aspects of the cardiovascular system and its regulation show robust day/night rhythms in healthy people, including increases in catecholamine levels, heart rate, and blood pressure^{15, 29–32} during the beginning of the daily active span. These rhythms provide a biological advantage to healthy individuals, but the rhythmic increases in sympathoadrenal signaling, heart rate, and blood pressure might also contribute to increased risk for myocardial infarction, stroke, arrhythmias, and SCD in unhealthy individuals.^{33–38} In other words, circadian rhythms in catecholaminergic signaling that are advantageous in healthy individuals might increase the risk for deleterious events in people living with cardiovascular disease. Further dissection of how these rhythms interact with people living with coronary vascular disease, different types of cardiomyopathies and genetic arrhythmias, as well as other underlying causes of SCD will be an important step for tailoring the timing of disease-specific treatments with circadian-dependent phenomena to achieve optimal therapeutic and preventive effects.³⁹

Opportunity: Identify and investigate subsets of at-risk persons distinguished by sex, race, age, cardiac pathology, treatments, genetics, circadian disruption, etc. and determine in which subsets physiological changes across the circadian cycle confer sudden cardiac death risk.—The demographics of people living with different types of heart disease span across the spectrum of sex, age, and race. Generally speaking, children have earlier chronotypes (preference for the timing of the sleep and wake routines). The chronotype preference gets progressively later during adolescence until ~20 years of age.⁴⁰ Females on average have shorter intrinsic circadian periods than males, which likely contributes to their earlier entrained circadian phases.^{41, 42} Across adulthood, females continue to have earlier chronotypes than males. In older age, the chronotypes in males shift earlier. However, these changes are not due to changes in the intrinsic period of the circadian system^{41, 43} but rather due to changes in sleep-wake homeostatic processes.^{44, 45}

Some small studies associate differences in the circadian system with racialized categories. African Americans were found to entrain to light phase advances or delays differently than European Americans, and African Americans were reported to show shorter intrinsic circadian periods.⁴⁶ These racialized categories have no biological basis, so it is important to determine whether these differences stem from dynamic environmental factors, such as disparities in socioeconomic status, access to health and education, as well as the impacts of marginalization and discrimination.^{47, 48} Future studies designed to clearly separate how biological, genetic, and environmental factors contribute to the circadian system, and how these factors relate to the risk of SCD, will be important for developing effective mitigation strategies.

Gap 2: There is a lack of methodology to quantify circadian health in people and human tissues that is needed to assess the impact of deviations from normal on sudden cardiac death risk.

A considerable amount of research indicates different etiologies of SCD may associate with different times of vulnerability across the 24-hour period. This research leads to several

untested hypotheses. For example, in those predisposed to SCD, is the temporal pattern in risk of SCD a:

- i. Direct consequence of the phasing of endogenous circadian processes at the cardiovascular level?
- ii. Direct consequence of the phasing of endogenous circadian processes at the central pacemaker level?
- iii. Direct consequence of the timing of environmental or behavioral triggers?
- iv. Combined consequence of the phasing of endogenous circadian processes at the cardiovascular or central pacemaker level with the particular timing of environmental or behavioral triggers?
- v. Consequence of circadian disruption due to atypical times of sleep/wake cycle, rest/activity cycle, meal/fasting cycle and/or other lifestyle behaviors in time⁴⁹ that alters the normal synchronization of physiological processes across the cardiovascular system and/or the central pacemaker?

Opportunity: Develop new biotechnological tools (e.g., wearables, bioinformatics) to interrogate day-night rhythmic phenotypes.—There are opportunities to develop new technologies and to reimagine existing ones in order to identify heart rhythms and behaviors that reliably predict arrhythmic events and SCD in at-risk populations. For example, there is an increasing use of implantable loop recorders (ILRs) that allow continuous monitoring of people at higher risk for SCD, such as those with hypertrophic cardiomyopathy or long QT syndrome. These devices track clock and calendar time occurrence of arrhythmias, but do not provide understanding of the circumstances that predispose vulnerability to cardiac arrest and SCD. There are opportunities to complement existing ILR monitoring with other assessment technologies to more comprehensively and continuously track key variables. For example, sleep monitoring for sleep architecture, sleep duration, and sleep disorders, obtained in conjunction with ILR monitoring, will help determine if changes in sleep characteristics immediately precede, and perhaps precipitate in, potentially fatal cardiac events.

Similarly, incorporation of unobtrusive blood pressure monitoring options would add to the understanding of risk. For example, the day/night pattern of blood pressure is generally characterized by peak values during the late afternoon/early evening and lowest values during sleep. The sleep-period decline in systolic blood pressure relative to wake-period usually amounts to -10 to -20% , and has been termed the sleep-time blood pressure dipping pattern.⁵⁰ However, in sleep apnea and certain other medical conditions the day/night pattern is different such that the sleep-time systolic blood pressure fails to decline (or rises) substantially from wake-time levels. This may indicate a disruption of neuroendocrine and other circadian rhythms that regulate the day/night pattern of blood pressure.^{51–55} This sleep-time ‘non-dipping’ blood pressure pattern constitutes an increased risk for myocardial infarction, stroke and other cardiovascular morbid and mortal events.⁵⁶ The role of altered circadian patterning of the blood pressure rhythm and the underlying factors that result in elevating the risk for SCD awaits exploration. It is noteworthy that, in comparison to upon

wakening, ingestion of blood pressure-lowering medications before bedtime, particularly angiotensin converting enzyme inhibitors and angiotensin receptor blockers, can normalize the elevated sleep-time systolic blood pressure, improve the 24 hour non-dipping profile, and reduce cardiovascular disease morbidity and mortality.^{56–60} This example illustrates the potential for rhythm-based chronotherapy that mitigates SCD risk. We anticipate that identifying circadian vulnerabilities or disruptions in circadian rhythms linked to SCD will inform novel chronopreventive strategies (analogous to those developed for people with ‘non-dipper’ hypertension).^{61, 62}

Opportunity: Develop and validate biomarkers to assess behavioral, central, and peripheral (including cardiac) circadian rhythms and assess correlations with SCD risk.—Current sensor-equipped wearable tracker hardware used in conjunction with interpretative software is capable of accurately monitoring environmental, behavioral and biological variables, including movement/activity, sleep, behaviors such as meal timing, heart rate, heart rate variability, blood pressure, body temperature, and oxygen partial pressure. Herein lies an opportunity for the additional technologies that also allow continuous monitoring of relevant cardiovascular and behavioral variables coded by clock time and calendar date. Such data will generate the databases required for proper investigation of mechanisms for the risk of SCD. As the science develops, the hope is to move from simply assessing time of day events to assessing endogenous circadian time to understand the circadian influence on SCD.⁶³

New technologies that enable the unencumbered non-invasive continuous monitoring of the electrocardiogram, blood pressure and other variables may identify patterns that predict future SCD events. Potentially relevant variables include body temperature, activity, blood glucose, and more unconventional variables that may fluctuate with circadian phase and/or exposure to behavioral/environmental stressors (e.g., the changes in the gut transcriptome and tissue/cellular expression of circadian genes). Technology to ascertain these and other metrics should be developed in order to collect data from large samples of subjects, including children and adults of both sexes.

Opportunity: Create large-scale human datasets that include chronobiological measurements and cardiovascular outcomes.—This opportunity can include projects to obtain data through public-private collaborations and industry-initiated/sponsored trials. For example, the National Institutes of Health *All of Us* program (<https://allofus.nih.gov/>) aims to enlist one million participants to build one of the most diverse health databases in history. This database will consist of clinical, genomic and mobile health data to enable exploration of biological, lifestyle and environmental aspects of health, disease pathogenesis, treatment response, and health promotion and disease prevention. Application of advanced computational analyses of large databases, composed of biological and ambient entries properly qualified for circadian time, should involve machine learning-based artificial intelligence methods to identify specific cardiovascular, sleep, and behavioral variables that predict increased risk for SCD. Some of the desired variables can be acquired by currently available consumer-wearable monitoring devices, however, more advanced and standardized high-performance clinical-grade technologies that enable around-the-clock

assessment of multiple meaningful biological, behavioral and environmental variables are lacking and urgently required.

Gap 3: There is a lack of understanding of the impact of circadian rhythm disruption on risk for SCD.

Knowing more about circadian rhythms in healthy populations and how they impact or are impacted by diseases that are associated with SCD will promote development of behavioral and environmental interventions and novel pharmacotherapies. For example, disruptions in certain behavioral rhythms can likely be normalized through behavioral interventions to reduce SCD risk. These interventions could include optimizing the timing of eating, exercise, or the taking of medications. The possibility also exists that advanced drug delivery systems can be positioned in cardiac tissue that are responsive to the cellular circadian clock mechanism to release therapeutics at the optimal biological times. This line of research may identify new targets for drug therapy and lead to strategies for drug administration to correct disrupted rhythms that confer risk of poor outcomes (similar to non-dipper hypertension discussed above) and/or serve to counter the increased risk of adverse cardiovascular consequences in vulnerable populations that suffer disruptions in circadian rhythms (e.g., shift workers, people with disrupted sleep, sleep/wake disturbances, etc.).

Opportunity: Investigate the impact of day/night rhythm misalignment, alteration of circadian period, phase, and/or amplitude on SCD risk.—Data from carefully controlled human studies show that markers of inflammation, coagulation, blood pressure, and heart rate exhibit endogenous circadian variation in healthy young subjects.⁶⁴ Furthermore, analysis of human cardiovascular tissue samples reveals daily variation in the expression of specific cardiac channels and autonomic receptors.^{64, 65} These factors are likely involved in both *directly* triggering cardiac arrest events in vulnerable individuals and in the long-term development/progression of underlying heart disease. In addition to the role of the circadian system and daily rhythms in the timing of serious adverse cardiovascular events, there is a growing body of evidence indicating that circadian disruption is a risk factor for SCD.⁶⁶

Environmental circadian misalignment occurs as a consequence of disruptions in the temporal relationship between the circadian system relative to environmental cycles. Behavioral circadian misalignment occurs because of a disruption in the temporal relationship between the circadian system relative to behavioral cycles. Internal misalignment occurs because of a disruption in the temporal relationships between different circadian oscillators (e.g., the central circadian pacemaker and peripheral oscillators and/or misalignment between different peripheral oscillators). Environmental, behavioral and internal circadian misalignment are not mutually exclusive. For example, if the timing of the light/dark cycle and the eating/fasting cycle are disturbed, internal misalignment can develop. In this case, the timing of food intake alters certain peripheral clocks, such as in the liver or skin, while the clock in the SCN maintains synchronization by the light/dark cycle.^{67, 68} In healthy human subjects, highly-controlled studies demonstrate that misalignment between the central circadian pacemaker relative to the behavioral and environmental cycles worsens several parameters associated with increased risk of

cardiovascular disease, including increases in blood pressure and inflammatory markers (hsCRP, IL-6, TNF- α).^{24, 66, 69–72} Epidemiologic studies of shift workers showing increased risk for diabetes, hypertension, and myocardial infarction are consistent with these data. However, key gaps in the current state of science revolve around being able to reliably quantify the influence of circadian disruption on SCD risk remain. This includes but is not limited to distinguishing and understanding the mechanisms mediating the SCD risks resulting from environmental and behavioral circadian misalignment as opposed to the SCD risks resulting from the internal circadian misalignment.

Opportunity: Determine if biomarkers that reflect circadian disruption are robust predictors of SCD and whether restoring circadian rhythm synchrony lowers risk for SCD.—

The study of circadian misalignment requires a basis for defining normal circadian alignment. One of the key barriers in advancing the science of chronobiology is the lack of an accepted clinical biomarker for circadian phase. In laboratory and controlled field settings, dim light melatonin onset (DLMO) is the gold-standard biomarker for assessing the phase of the central clock in the SCN. However, the measurement of DLMO requires repeated samples over a span of several hours while participants remain in dim light conditions. Another limitation is that it does not reveal the phase of the circadian clocks in different cell populations. As the use of β -blockers can suppress the secretion of melatonin,⁷³ this already difficult test is often inappropriate for use in populations with underlying cardiac disease, including those most at risk for SCD. Moreover, even in the laboratory setting there are no established, easily accessible, markers defining circadian phase in the different tissues and organs relevant to cardiac disease.

Several research groups are actively searching for alternative biomarkers that require fewer samples, are robust to various diets, medications, and genomic backgrounds, and do not require dim light conditions. Preliminary studies on blood based molecular circadian biomarkers have been reported.^{74–76} However, none have been validated across a wide variety of patient populations, clinical conditions, and behavioral perturbations (e.g., shift work, altered mealtimes, etc.). In addition, to date, none of the proposed diagnostics focused on the markers for the circadian clock or circadian molecular outputs in peripheral tissues that are most relevant to SCD (e.g., vasculature, heart muscle, sino-atrial node, His-Purkinje system).

Beyond the assessment of circadian phase, measures of circadian disruption are particularly important for clinical study. Circadian disruption is most common in the setting of night shift work but can occur in almost any setting. This is especially true with the widespread use of light at night which shifts the SCN central phase quickly, while peripheral clocks may take longer to re-synchronize to the new central circadian phase (about 1 hour per day, depending on the intensity and circadian timing of light exposure).^{19, 77}

The discrepancy between biomarker estimated central circadian phase and behavioral and/or environmental cycles is a natural measure of molecular, behavioral and environmental circadian misalignment. However, measures of local clock function in cardiac tissue or measures that better describe the period, phasing and amplitude of specific processes may have more utility in predicting and explaining risk. Ultimately the specific molecular

rhythms important to SCD development and the measures of circadian dysfunction that best predict risk will require dedicated clinical studies. Similar studies are required to identify the underappreciated impacts of existing risk factors (e.g., geographical setting, alcohol, drugs, smoking/vaping, etc.) or interventions that improve these circadian measures on cardiovascular outcomes.

Conclusion

A clearer picture of the functional role for normal circadian rhythms in healthy cardiovascular function requires new investigations with an emphasis on circadian rhythmic synchrony and alignment, and the potentially pathologic impact of desynchrony and misalignment, at individual and population levels. Chronobiological studies in populations at risk for SCD will likely yield the highest translational value. Challenges remain, but recent technological advancements, as well as the identification of biomarkers, will facilitate studies that determine how behavioral, environmental and circadian rhythms impact the risk for SCD. With focused attention, relatively quick advances can be made, especially in terms of identifying chronotherapeutic and chronopreventive strategies. These studies may also identify new pharmacological therapies that reduce the risk of SCD, as well as the progression of cardiovascular diseases that predispose to SCD in populations living with circadian disruption.

Acknowledgments

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services. B.P.D. was supported by NIH grants R01HL153042 and R01HL141343. A.L.G. was supported by NIH grant HL122010. F.A.J.L.S. was supported by NIH grants R01HL118601, R01DK099512, R01DK102696, and R01DK105072 and R01HL140574. Dr Shea was supported by NIH grant R35 HL155681. Several of the images were prepared using BioRender.com.

Non-standard Abbreviations and Acronyms

SCD	Sudden cardiac death
SCN	Suprachiasmatic Nucleus
ILRs	implantable loop recorders
FDA	Food and Drug Administration
NIH	National Institute of Health
hsCRP	Highly sensitive C-reactive protein
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor alpha
DLMO	Dim light melatonin onset

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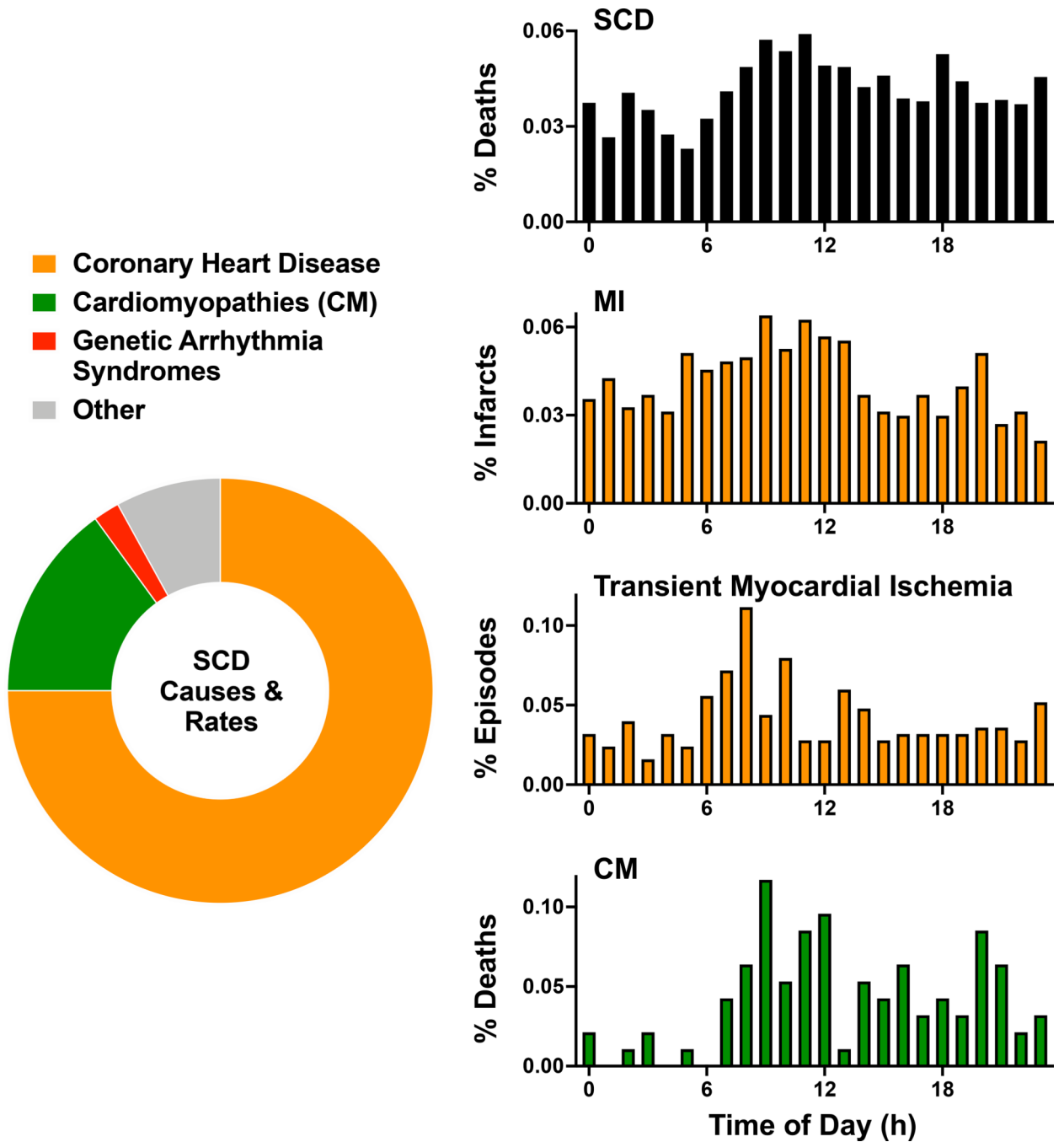


Figure 1. Several types of cardiovascular disease exhibit a time of day incidence in SCD or events.

The left graphic shows the causes and rates for SCD by several different types of cardiovascular disease (data from² DOI: 10.1161/CIRCRESAHA.116.304521). Shown on the right is the 24-hour incidence of SCD, myocardial infarction, transient myocardial ischemia episodes, or SCD in people with hypertrophic cardiomyopathy (data from⁵ DOI: 10.1161/01.cir.79.4.733 and¹⁰ DOI: 10.1016/0735-1097(94)90384-0).

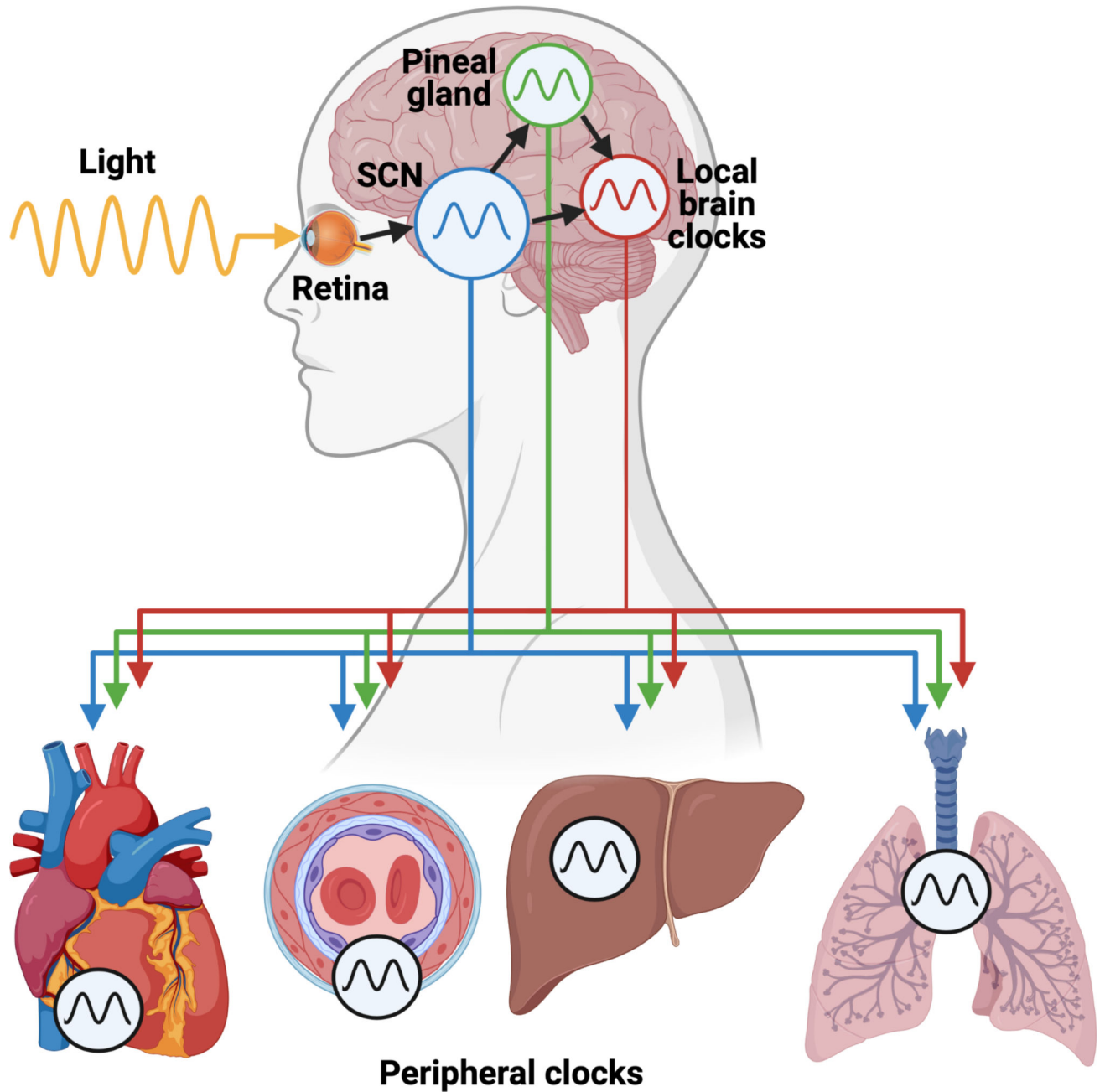


Figure 2. Circadian rhythms are generated by cell autonomous clocks, present in every nucleated cell in the body, that resonate with a periodicity of ~24 hours.

Clock systems are organized with a master pacemaker role for the suprachiasmatic nucleus (SCN) in the hypothalamus, which directly or indirectly synchronizes (red arrows) circadian rhythms in other tissues and systems throughout the body. Timing in the SCN is controlled (entrained) by direct retinal input to the SCN from light-sensitive retinal ganglion cells. This system enables the organism to adapt (entrain) to changing external light-dark cycles. Pacemaker neurons, in turn, entrain neurons in several other brain regions, including the

pineal, and, as an ensemble (red, green, blue arrows), central nervous system clocks produce rhythmic signals to regulate peripheral tissue circadian clocks throughout the body.

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Table.

The identification of knowledge gaps and opportunities for understanding circadian mechanisms contributing to SCD clearly requires some definitions as a framework. This table provides operational definitions to several of the terms used throughout this paper. We recognize disciplines sometimes use the same term to describe different aspects of chronobiology, and although an interdisciplinary consensus for definitions is warranted, this task is beyond the scope of this report.

<p>Day/night rhythms: ~24-hour rhythms caused by a combination of behavioral rhythms (e.g., postural change and increased activity upon awakening, daily sleep/wake cycle, daily fasting/feeding cycle), environmental rhythms (daily cycles in light, temperature and ambient air composition) and ~24-hour internal circadian rhythms.</p> <p>Circadian rhythm: Throughout this article, we refer to circadian as being driven by the internal body clock (ie, endogenous) with a period of about 24 h. Circadian rhythms persist even in the absence of the effects of the environmental or behavior-related cues but can be entrained by them. Until researchers begin to use the term consistently it is advisable to read the protocols of all studies in this area for appropriate data interpretation.</p> <p>Chronotherapeutic strategies: Timing of medications or medical intervention according to circadian or day/night rhythms to optimize beneficial therapeutic and/or minimize or avert adverse effects.</p> <p>Chronopreventive strategies: Timing of medications, behavioral, or other medical interventions to avert pathological outcomes, including morbidity and mortality to match the timing of other inputs, such as a repetitive physiological trigger or rhythmic signal.</p> <p>Entrainment: The synchronization of a self-sustaining oscillation (such as a circadian rhythm).</p> <p>Circadian synchrony: State of circadian system when two or more rhythmic variables exhibit periodicity with the same frequency or with frequencies that are integer multiples or submultiples of one another.</p> <p>Circadian alignment: The state of 2 or more processes to start at the same time (or have a consistent phase relationship) or to occur at a normal or optimal phase angle.</p> <p>Circadian disruption: The action of acutely or chronically altering one or more circadian rhythms from having a normal period, phase and/or amplitude (circadian system disruption, clock disruption, perturbations in circadian rhythms, genetic circadian clock disruption, circadian desynchronization, circadian misalignment).</p>
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