Consequences of Circadian and Sleep Disturbances for the Cardiovascular System

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ABSTRACT
Circadian rhythms play a crucial role in our cardiovascular system. Importantly, there has been a recent flurry of clinical and experimental studies revealing the profound adverse consequences of disturbing these rhythms on the cardiovascular system. For example, circadian disturbance worsens outcome after myocardial infarction with implications for patients in acute care settings. Moreover, disturbing rhythms exacerbates cardiac remodelling in heart disease models. Also, circadian dyssynchrony is a causal factor in the pathogenesis of heart disease. These discoveries have profound implications for the cardiovascular health of shift workers, individuals with circadian and sleep disorders, or anyone subjected to the 24/7 demands of society. Moreover, these studies give rise to 2 new frontiers for translational studies revealing the profound adverse consequences of disturbing these rhythms on the cardiovascular system. For example, circadian rhythms exacerbates cardiac remodelling in heart disease models. Also, circadian dyssynchrony is a causal factor in the pathogenesis of heart disease. These discoveries have profound implications for the cardiovascular health of shift workers, individuals with circadian and sleep disorders, or anyone subjected to the 24/7 demands of society. Moreover, these studies give rise to 2 new frontiers for translational research:

1. circadian rhythms and the cardiac sarcomere, which sheds new light on our understanding of myofilament structure, signalling, and electrophysiology; and
2. knowledge translation, which sheds new light on our understanding of myofibrillar structure, signalling, and electrophysiology; and

Also, new promising approaches to improve the management and treatment of cardiovascular disease. Reconsidering circadian rhythms in the clinical setting benefits repair mechanisms, and offers new promise for patients.

RÉSUMÉ
Les rythmes circadiens jouent un rôle crucial dans notre système cardiovasculaire. Notamment, une récente avalanche d'études cliniques et expérimentales révélant les conséquences indésirables des perturbations de ces rythmes sur le système cardiovasculaire ont été réalisées. Par exemple, la perturbation des rythmes circadiens détériore les résultats cliniques après l'infarctus du myocarde des patients en soins de phase aiguë, de plus, la perturbation des rythmes exacerbe le processus de remodelage cardiaque des modèles de cardiopathie. Aussi, la dyssynchronie circadienne est un facteur causal dans la pathogénèse de la cardiopathie. Ces découvertes ont de profondes conséquences sur la santé cardiovasculaire des travailleurs de nuit, des individus ayant des troubles du rythme circadien et du sommeil, ou de tout individu soumis tous les jours 24 heures sur 24 aux exigences de la société. En outre, ces études mettent en exergue 2 nouvelles frontières de la recherche translationnelle:

1. les rythmes circadiens et le sarcome cardiaque, lequel jette un nouvel éclairage sur notre compréhension de la structure des myofilaments, de la signalisation et de l'électrophysiologie; 2. l'application des connaissances, qui comprend la découverte des biomarqueurs (chronobiomarqueurs), le meilleur moment des thérapies (chronothérapie) et d'autres nouvelles approches prometteuses pour améliorer la prise en charge et le traitement de la maladie cardiovasculaires. La reconsideration des rythmes circadiens en milieu clinique favorise les mécanismes de réparation et s'avère prometteuse pour les patients.

Jürgen Aschoff was a physician, scientist, and cofounder of the field of circadian biology. He introduced the notion that day and night (diurnal) rhythms in physiology are a fundamental feature in most living organisms including humans. We now know that rhythms are regulated by the circadian system, by orchestration in the hypothalamic suprachiasmatic nucleus, and through neural and hormonal outputs to all organs including the heart (Fig. 1A). Mechanistically, an exquisite underlying cellular clock mechanism has been identified, which controls molecular rhythms in virtually all cells including cardiomyocytes (Fig. 1B). Over the past 5 decades numerous clinical and experimental studies have revealed a crucial role for the circadian system in regulating healthy physiology. Most recently, studies by our group and others have shed light on the profound adverse health consequences of circadian disturbances, underlying cardiovascular, cancer, metabolic, respiratory, psychiatric, and other disorders. In this review we focus on the consequences of circadian disturbances on the pathogenesis and pathophysiology of heart disease.
Circadian Biology and Normal Cardiovascular Physiology

Circadian rhythms in heart rate and blood pressure

Circadian rhythms are important for daily cyclic variation in mammalian physiology, for example our heart rate (HR) is highest during wake and lowest during sleep. Blood pressure (BP) also displays a daily rhythm, indeed, Floras and colleagues documented for the first time the remarkable BP surge that occurs at the time of waking and morning activity. BP is highest in the morning and decreases progressively (approximately 10%) to reach a nadir during sleep. These rhythms are consistent with the diurnal biases of our autonomic nervous system, which oscillate over 24-hour periods. Thus our cardiovascular physiology exhibits striking time of day-dependent oscillations. Remarkably, diurnal variations in HR and cardiac contractility observed in vivo still persist ex vivo, for example, when rodent hearts are perfused on a Langendorff apparatus. Thus it is not just the neurohormonal axes that contribute to time of day cardiac physiology, but also the intrinsic circadian properties of the heart. Over the past decade this has given rise to numerous experimental studies that show a direct role for the circadian mechanism on our daily cardiovascular physiology, as is demonstrated experimentally in rats and mice.

Daily timing of onset of adverse cardiovascular events

Adverse cardiovascular events are a leading cause of death worldwide and do not occur at random times throughout the day. An early morning peak of acute myocardial infarction (MI) was first reported in 1985, and in the decades since, despite changes in lifestyle and advances in medicine, the pattern of morning excess of MI persists. A diurnal pattern also occurs for infarct size, stroke, angina, ventricular tachyarrhythmia, defibrillation energy requirements, ventricular refractoriness, and sudden cardiac death. Physiologically, sympathovagal balance is thought to play a causal role, because patients with autonomic nervous system dysfunction do not exhibit the early morning peak in timing of onset of MI. Several studies have highlighted additional factors, many under circadian control, which increase the risk of adverse cardiovascular events, including diurnal rhythms in platelet activity, thrombosis or thrombolyis, and endothelial function. Mechanistically, a direct role for the circadian mechanism underlying time of day dependence has been demonstrated in humans and animal models.

Diurnal variations in cardiomyocyte metabolism

As described, cardiac function displays a time of day effect, driven in part by the sympathetic environment and the neurohormonal milieu. However, at the myocyte level, there is considerable new evidence that intrinsic cellular properties also occur in a circadian manner, as has been exquisitely detailed in studies by Young and colleagues. To summarize, this is especially evident from the ex vivo perfused rat or mouse heart models, which demonstrate persistence of time of day variations in cardiac metabolism, even in the absence of neural and hormonal cues. Day/night variations in cardiac metabolism allow the heart to switch between different substrates (mainly glucose and fatty acids) for energy sources depending on availability over the course of 24-hour periods. These intrinsic cardiomyocyte processes are facilitated in part by the cardiomyocyte-specific circadian clock mechanism. This circadian mechanism regulates messenger RNA (mRNA) and protein expression of key metabolic factors in cardiomyocytes as described herein, thus controlling cellular processes in a time of day-dependent manner.

Circadian genomics

The heart is genetically a different organ in the day vs the night. The first large-scale microarray study to demonstrate this revealed that approximately 8% of genes are rhythmic in murine hearts under circadian (constant dark) conditions.
However, because humans (and medicine) exist in a diurnal and not circadian environment, we showed that approximately 13% of genes in murine hearts are rhythmic under normal day and night conditions. These genomic experiments recapitulate earlier findings of individual clock gene cycling in polymerase chain reaction analyses, and moreover, identify many new rhythmic genes important for cardiac growth, renewal, transcription, translation, signalling pathways, and metabolism. Our circadian heart microarray data (and that of other researchers) are available through an open access Web site created by the Hogenesch laboratory (Circadian Expression Profiles Data Base, Circa DB, http://bioinf.itmat.upenn.edu/circa/). Rhythmic cycling of the core circadian mechanism genes has also been recently demonstrated in human heart tissue, in polymerase chain reaction analyses. Consistent with these observations is the persistent 24-hour rhythmic oscillations in bioluminescence in heart and vascular tissue explants from transgenic rats in which luciferase expression is driven by the circadian mechanism factor, Period 1 (Per1). Moreover, rhythmicity has also been shown to occur at the cellular level, in cardiomyocytes, vascular smooth muscle cells, endothelial cells, and fibroblasts in culture. It is worth noting that researchers generally perform rodent studies during the light period, during rodent sleep time, and results are frequently compared with human wake time. These molecular studies clearly demonstrate that timing of functional assessments is highly critical in interpreting experimental findings. In summary, the cell types in the heart possess circadian clock mechanisms that regulate a variety of clock-controlled output genes, which in turn influence the time of day processes essential for heart structure and function.

Circadian proteomics

Because it is the proteins and not directly the mRNA that underlies fundamental biochemical processes in cells, studies have recently begun to explore circadian variation in the cellular proteome. We found that approximately 8% of the soluble cardiac proteome exhibits diurnal variation in murine heart, using a large-scale 2-dimensional difference in gel electrophoresis and mass spectrometry approach. The circadian mechanism plays a role in protein abundance in the heart; cardiomyocyte-specific Clock mutant mice have altered diurnal abundance of proteins, including many rate-limiting enzymes crucial for vital metabolic pathways in the heart. In terms of how time of day protein abundance is controlled, we reported that approximately half of the diurnal variation in the cardiac proteome can be accounted for by underlying rhythmic changes at the mRNA level. Our findings are consistent with a previous report by Reddy et al., who similarly observed approximately 50% of mRNA fluctuations underlying the hepatic proteome. Most recently, Luck et al. developed a statistical model that showed that rhythmic production and degradation (half-life) at the mRNA and protein levels underlies daily protein abundance. Additional mechanisms that regulate diurnal molecular rhythms are glucocorticoid control of transcription, and time of day variations in chromatin architecture. Thus, there is a dynamic nature to the cardiac proteome, which underlies diurnal variations in heart function.

Experimental Models of Circadian Disruption and Consequences for the Cardiovascular System

As highlighted in the preceding section, circadian rhythms are fundamentally important for cardiovascular health. The heart displays clear differences in time of day organ, cellular, and molecular physiology. Questions arise, therefore, as to what happens when these rhythms are disturbed. Circadian rhythm disturbances can have multiple deleterious effects on organ physiology, with profound clinical implications for cardiovascular and other diseases. In this section we focus on experimental studies investigating the profound adverse effects of circadian rhythm disturbance on the cardiovascular system.

Diurnal disturbance worsens outcome after MI

MI triggers a temporally orchestrated inflammatory response designed to clear the infarct of dead cells and debris, and at the same time activates reparative pathways for fibrosis and scar formation. We postulated that the circadian mechanism plays a key role in immune cell recruitment and infarct healing after MI. That there is daily cycling of peripheral blood cells, diurnal reactivity of immune cells, and a circadian mechanism in immune cells provides indirect support for this hypothesis. Our recent study directly recognized, to our knowledge for the first time, that the circadian mechanism plays a causal role in immune cell recruitment to infarcted myocardium, and that disturbing this mechanism worsens outcome after MI. Mice were infarcted using left anterior descending coronary artery ligation (MI model), and randomized to either a normal diurnal or disrupted light:dark environment for 5 days, and then maintained in normal diurnal conditions. Short-term diurnal disruption altered innate immune responses crucial for scar formation, leading to maladaptive cardiac remodelling (Fig. 2). One of the most intriguing findings is a role for the circadian mechanism factor CLOCK in recruiting innate immune cells after MI. This study has clinical relevance, because circadian and sleep disturbances can impair recovery in modern intensive care units. Reconsidering how we practice medicine, by maintaining the diurnal environment and patient biological rhythms, provides a promising non-pharmaceutical approach to improve patient outcomes in acute clinical care settings.

Diurnal disturbance worsens cardiac remodelling

The adverse consequences of diurnal disturbance on pre-existing heart disease was first demonstrated by Turek and colleagues, who revealed the deleterious effects on survival in cardiomyopathic hamsters subjected to chronic shifts in the light and dark cycle. We showed that diurnal rhythm disturbance exacerbates cardiac remodelling in mice with pressure overload-induced cardiac hypertrophy; and importantly, that the adverse remodelling only ceased when the animals were returned to their normal diurnal cycle. Thus, altering the photoperiod to one in which animals cannot entrain alters the relationship between the light and dark cycle, endogenous physiology, and cardiac gene and protein levels, such that individuals are “out of sync” with their environment. This has direct consequences on cardiac
physiology and pathophysiology, exacerbating underlying heart disease.

Circadian dyssynchrony causes heart disease

The important consequences of circadian dyssynchrony on the heart are perhaps best exemplified by the +/-tau hamster studies. These animals carry a mutation in the circadian clock mechanism gene, casein kinase 1 epsilon, such that they exhibit an internal circadian period of approximately 22 hours, even though they live in a 24-hour world.111 The +/-tau heterozygotes exhibit abnormal entrainment to the 24-hour diurnal environment (earlier onset and a more fragmented activity profile),112 and reduced longevity, compared with their wild type littermates.113 In terms of cardiovascular consequences, the Sole and Ralph laboratory demonstrated that circadian disorganization in the +/-tau hamsters is a causal factor in the pathogenesis of dilated cardiomyopathy.114 Conversely, if the animals are housed in diurnal cycles appropriate for their genotype (22 hours), then rhythms normalize and the heart disease is prevented.114 Notably, the tau/tau homozygotes have a 20-hour period and do not entrain to a 24-hour light and dark cycle and thus they do not develop heart disease.114 Thus, these studies demonstrate the importance of synchrony between the intrinsic circadian period and the external light-dark environment, highlighting that abnormal entrainment by circadian dyssynchrony plays an aetiologic role in the pathogenesis of heart disease.

Circadian gene mutations and heart disease

Additional lines of evidence further support the notion that circadian mechanism gene factors underlie cardiovascular pathophysiology: several recent studies are summarized herein. (1) Whole body brain and muscle ARNT-like 1 (BMAL1)-/- knockout mice exhibit a loss of diurnal variation in HR and BP,26 and develop dilated cardiomyopathy.66,116 (2) Cardiomyocyte-specific Bmal1 knockout mice also develop dilated cardiomyopathy even though the disturbance is only in the heart.66,116 (3) In gene mapping studies it was found that Bmal1 associates with hypertension loci in spontaneously hypertensive rats.117 (4) In a similar light, BMAL1 (and also neuronal PAS domain protein 2 [Npas2]) polymorphisms are associated with hypertension in humans.117,118 (5) Mice with
Circadian rhythms and insufficient sleep

Circadian rhythm disturbances are also relevant through their intersection with sleep because sleep is under both circadian and homeostatic control. Indeed, a role for circadian mechanism genetic factors on sleep has been recently discovered in humans. For example, familial advanced phase sleep syndrome is associated with a missense mutation in the clock component PER2, which alters the circadian period. These individuals go to sleep very early in the night time, and routinely wake up in the extreme early morning hours. Although a direct correlation between circadian factors that influence sleep and heart disease in humans has not yet been demonstrated, facts affecting sleep duration clearly have a direct effect on cardiovascular health. For example, in today’s society, 40% of North Americans do not achieve the recommended 7 hours of sleep, and short (<5 hours) or long (>9 hours) sleep durations are associated with an increased risk of heart disease. These findings are consistent with earlier reports of increased all-cause mortality risk (including ischemic heart disease) in individuals with sleeping patterns other than 7-8 hours per night. In addition to circadian mutations that cause sleep changes, circadian-coupled factors disturbed by inadequate sleep might mechanistically contribute to heart disease pathophysiology. Intriguingly, there are molecular consequences on diurnal gene expression in the heart with as little as one night of sleep deprivation. This was demonstrated in mice after 3, 6, 9, and 12 hours of sleep deprivation, which altered expression of 2470 genes in the heart in microarray analyses.

Chronotypes, social clocks, and light at night

Circadian rhythms in some physiologic functions vary between humans (eg, core body temperature, melatonin phase), leading to classifications of early/morning or late/ evening chronotypes. Intriguingly, chronotype might influence cardiovascular disease, because evening types appear to be more at risk for cardiovascular changes (hypertension, HR, BP) compared with morning types. A later chronotype is also associated with social jet lag—the misalignment of biological and social clocks—and prevalence of social jet lag in apparently healthy individuals might contribute to cardiovascular risk. Light at night including that from light-emitting diodes in television and computer screens has broad consequences for our health, and is the subject several interesting recent reports. These studies are relevant to contemporary society and shed new light on how our circadian phenotypes, lifestyle choices, and the diurnal environment can affect cardiovascular health and disease.

New Frontiers: Circadian Rhythms and the Cardiac Sarcomere

In addition to the mentioned experimental and clinical discoveries, there are new frontiers for circadian rhythms research important to our understanding of the cardiovascular system. The first involves circadian rhythms and the cardiac sarcomere, which is the main contractile apparatus in the heart. These studies give rise to new understanding of myofilament structure, signalling, and electrophysiology, as detailed herein. 

Circadian rhythms and myofilament structure

Cardiac myofilaments mediate heart performance (Fig. 3) and recent studies indicate a role for the circadian mechanism in affecting myofilament and thus
cardiac function. For example, ex vivo rat hearts exhibit the greatest contractile performance during the animal wake vs sleep time, in Langendorff analysis. Conversely, this variation in performance is ablated in hearts of diurnal-disrupted mice. At a molecular level, day/night rhythms in cardiac myofilament activity are lost in cardiomyocyte-specific Clock mutant mice compared with wild type mice, thus further supporting the notion that cardiac contractile performance links to the circadian mechanism. That there are significant disruptions in sarcomere architecture in Bmal1-/- mice provides further support for this notion. Our group also demonstrated a functional correlation between myofilament activity and protein phosphorylation as one mechanism for regulating diurnal myofilament function in the murine heart. Most recently we demonstrated that the expression of murine cardiac Titin-cap (Tcap, telethonin), a key regulator of sarcomere structure and function, is regulated by the circadian mechanism transcription factors CLOCK and BMAL1. In a similar light, Andrews and colleagues have shown links between skeletal muscles and the circadian clock mechanism, and a pathway by which changes in myofilament function can influence the ability of the heart to respond to changes in driving factors.

**Circadian rhythms and myofilament signalling**

Cyclic adenosine monophosphate-dependent protein kinase (PKA) targets the myofilament complex (troponin I, myosin binding protein C, titin, and others) and thus has a powerful ability to affect myofilament function. PKA gene expression is regulated by the cardiomyocyte clock, which might help explain diurnal variations in myocardial contractility. Additionally, there is diurnal variation in β-adrenergic receptor activation, a transmembrane receptor coupled with PKA activation in cardiac myocytes. Diurnal disruption decreases myofilament protein phosphorylation by PKA after MI in mice. Together, these findings show the importance of circadian variations in the β-adrenergic-PKA cascade, for myofilament regulation partly under control of the cardiomyocyte clock mechanism, and a pathway by which changes in myofilament function can influence the ability of the heart to respond to changes in driving factors.

**Circadian mechanism and cardiac electrophysiology**

As alluded to herein, the circadian mechanism plays a role in cardiac contractility via time of day fluctuations in contractile proteins. Mechanistically, this might also be regulated intrinsically by ion channels in the heart that influence myofilament activation, some of which exhibit diurnal variation. Time of day-dependent oscillations have been reported in the heart for the voltage-dependent potassium channels $K_{v1.5}$ and $K_{v4.2}$, and the L-type voltage-gated calcium channel subunit $VGCCa1D$. Also, L-type calcium channel current densities increase during the active period, which is consistent with the nocturnal elevation in murine HR. Moreover, circadian variations in potassium channel interacting protein-2 affect potassium channel opening in a manner that is consistent with changes in action
potential duration and circadian variations in HR. In vivo, the kruppel-like factor 15 (circadian output gene) knockout mice display increased susceptibility to ventricular arrhythmias, and reduced expression of potassium channel interacting protein 2. Finally, there is loss of the rhythmic sodium channel voltage-gated type V α subunit, and increased susceptibility to arrhythmias, in inducible cardiomyocyte-specific Bm41−/− mice. These studies provide new insights for understanding the diurnal nature of cardiac electrophysiology, HR regulation, and arrhythmias.

New Frontiers: Translational Chronocardiology

Another exciting new frontier is knowledge translation. This is important for rhythms research to have a beneficial effect on the quality of life for people with heart disease. One area of application is chronobiomarkers, in which temporal gene (microarray) and protein (proteomic) metadata are used to identify new biomarkers of heart disease. A second area of application is chronotherapy, which involves timing therapies to improve the management of cardiovascular (and other) diseases. These approaches and relevance to clinical cardiology are described in more detail herein.

Chronobiomarkers

Applying circadian concepts to clinical cardiology offers new opportunities for discovering biomarkers, with a variety of different technical approaches. For example, Ueda et al. estimate tissue time of day in mice by measuring expression of approximately 100 genes across a molecular time table in microarray analyses. Body time in mice and humans can also be estimated using metabolic studies. We discovered time of day biomarkers in murine cardiac hypertrophy using microarray profiling and a novel time series algorithm termed DeltaGene, and de novo chronobiomarkers in murine plasma samples over 24-hour periods. Collectively, these preclinical proof of concept studies are important for designing new approaches for biomarker discovery, by taking advantage of the body’s natural 24-hour molecular rhythms. Moreover, they have practical application for chronotherapy (described herein), which requires easily accessible markers of body time to optimize the timing of drug treatments.

Chronotherapy benefits (reverse) cardiac remodelling

Chronotherapy improves therapeutic efficacy (and possibly reduces toxicity) by timing treatments with our daily physiology. For example, in a preclinical study on heart disease, we showed that sleep-time administration of the short-acting angiotensin-converting enzyme inhibitor captopril markedly reduced cardiac remodelling in mice with pressure overload-induced cardiac hypertrophy; conversely, administration of wake time had no measurable benefit on heart damage. Mechanistically, the sleep-time benefit is associated with diurnal rhythms in the renin-angiotensin-aldosterone system and cardiac genes and proteins, which peak during the rodent sleep time. Indeed, there is significant potential for chronotherapy, because it has been recently reported that many best-selling drugs and the World Health Organization essential medicines have short half-lives for directly targeting gene pathways at specific times of day or night.

Hypertension chronotherapy

Chronotherapy can also be effective in the treatment of hypertension. Most people have a diurnal BP profile that exhibits a dip of approximately 10% at night. Conversely, hypertensive nondippers or normotensive individuals with attenuated nocturnal dips in BP have an increased risk of heart disease. Ambulatory BP monitoring, and especially covering the night time, is a useful prognostic indicator for heart disease, and is recommended by many international societies. Chronotherapy to treat hypertension at night helps to restore the day/night BP rhythms and reduces the risk of cardiovascular disease. For example, day and night drug administration manage daytime hypertension, however, only nighttime administration of ramipril, or telmisartan, or valsartan and amlopidine restores the nocturnal BP dip. Furthermore, the clinical trial termed Ambulatory Blood Pressure Monitoring in the Prediction of Cardiovascular Events and Effects of Chronotherapy (MAPEC) demonstrated prospectively that bedtime chronotherapy but not morning administration of antihypertensive medication improves BP control and reduces cardiovascular disease risk.

Chronotherapy and other cardiovascular conditions: obstructive sleep apnea, hemodialysis, aspirin

Chronotherapy also holds significant clinical applicability in other conditions associated with heart disease. For example, obstructive sleep apnea (OSA) is a common respiratory disorder of sleep, with underlying circadian-coupled mechanisms that if left untreated can lead to the development and exacerbation of heart disease and heart failure. Conversely, nocturnal continuous positive airway pressure (CPAP) therapy benefits patients with OSA and heart failure, reduces sympathetic activity, decreases BP during sleep, and improves left ventricular function. At a molecular circadian level OSA appears to cause circadian clock gene dysfunction, and nocturnal CPAP therapy helps to improve it. This was demonstrated by comparing Per1 mRNA expression in peripheral blood cells of healthy subjects, OSA patients, and OSA patients treated with CPAP.

Several additional lines of evidence further support the notion that timing of therapy benefits the cardiovascular system. For example, nocturnal hemodialysis of patients with cardio-renal disease reduces left ventricular hypertrophy and improves myocardial function, compared with patients given conventional daytime hemodialysis. In another study, low-dose aspirin taken at night reduced the circadian rhythm of platelet reactivity in healthy individuals; it is postulated that this might also reduce the risk of acute cardiovascular events during the peak morning hours. Thus, these time-dependent effects of therapies have significant potential for benefitting many patients in clinical settings.

Conclusions and Final Directions

Clinical and experimental studies demonstrate the important role of circadian rhythms for healthy cardiovascular
physiology. Disturbing of rhythms has direct adverse consequences on cardiac physiology and pathophysiology. Future studies will undoubtedly provide new insights into the mechanisms and molecular pathways that drive these pathologies. In terms of translation, significant opportunities exist to increase our understanding of circadian rhythms on cardiovascular disease. For example, experiments investigating circadian regulation of cerebrovascular conditions and stroke are virtually unknown despite this being the third leading cause of death in Canada with an estimated 50,000 strokes per year.\(^{200}\) Also, metabolic disorders are considered major risk factors for cardiovascular disease, and thus circadian rhythms research applied to prevalent clinical conditions such as diabetes and obesity could be fruitful areas of investigation. Determining the relationship between the circadian mechanism and cardiopulmonary conditions (eg, OSA and others) provides new opportunities to improve the diagnosis and treatment of heart and lung disease. Upcoming areas for knowledge translation include development of databases for patients with heart disease concurrent with circadian and/or sleep disorders, collecting circadian biometric data (eg, 24-hour HR and BP profiles, gene and protein biomarkers) in chronobiology and sleep clinics, and chronotherapeutic strategies to improve the effectiveness of existing treatments. Thus, circadian rhythms research advances our understanding of cardiovascular health and disease, and leads to novel strategies for management and treatment of heart disease in clinical settings.

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