Disruption of Circadian Rhythms and Sleep on Critical Illness and the Impact on Cardiovascular Events

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Abstract: The cardiovascular system exhibits significant daily rhythms in physiologic processes (heart rate, blood pressure, cardiac contractility and function), and molecular gene and protein expression. An increasing number of clinical and experimental studies demonstrate the circadian system is an important underlying mechanism that coordinates these rhythmic processes for the health of the cardiovascular system. However, what happens when rhythms are disturbed has been generally clinically unappreciated. Here we describe the profound adverse impact of disturbed circadian rhythms and sleep on the cardiovascular system, including recovery from myocardial infarction in acute care settings, shift work and heart disease, sleep disorders including obstructive sleep apnea, and cardiovascular pathophysiology associated with disturbed nocturnal blood pressure profiles. We also discuss therapeutic applications of circadian rhythms for the cardiovascular system. Cardiovascular disease is a leading cause of death worldwide, and applying circadian biology to cardiology (and indeed medicine in general) provides a new translational approach to benefit patients clinically.

Keywords: Cardiovascular, chronotherapy, circadian, intensive care, obstructive sleep apnea, shift work, sleep.

INTRODUCTION

The cardiovascular system exhibits dramatic time-of-day dependent rhythms in physiology including heart rate (HR), blood pressure (BP) and cardiac function. These daily oscillations are driven in part by the circadian system and its underlying molecular clock mechanism. In the first section of this review, we will briefly consider the current knowledge regarding circadian rhythms and healthy cardiovascular physiology. Importantly, a flurry of recent studies reveals that disturbing daily rhythms has profound adverse consequences for the cardiovascular system. The second section will focus on these new studies, elucidating how disturbing circadian rhythms worsens cardiovascular outcomes in acute care settings, for individuals with atypical work schedules (shift workers) or disturbed sleep, patients with obstructive sleep apnea, those with abnormal BP profiles, and therapeutic applications of circadian rhythms to benefit patients clinically. Finally, we discuss recent experimental studies using rodent transgenic models, which shed new light on our understanding of the mechanisms involved in circadian rhythm disturbance and cardiovascular disease.

CIRCADIAN RHYTHMS AND NORMAL CARDIOVASCULAR PHYSIOLOGY

Daily Rhythms in Cardiovascular Physiology

Life on earth is subjected to a 24 hour (h) day and night cycle, and circadian systems allow physiological processes to be synchronous with this cycle. That is, the circadian system helps us to entrain to the light and dark environment, to anticipate the differing physiologic demands of daily events [1-4] (Fig. 1A). The circadian system plays an especially important role in regulating the healthy physiology of the cardiovascular system [5-9]. For example, heart rate (HR) exhibits daily cyclic variation that is highest during wake time when we are active and lowest during sleep [10-12]. Blood pressure (BP) also exhibits daily rhythms, with a peak in the morning, progressive fall in the late afternoon and evening, and a nadir during sleep [13, 14]. These time-of-day variations are consistent with the sympathetic and parasympathetic biases of our autonomic nervous system (ANS) [15]. Experimentally, many rodent studies have helped to establish the role of not only the ANS as important in regulating these rhythms, but also the master circadian clock in the hypothalamic suprachiasmatic nucleus [3, 16-18]. For example, when this region is abolished in rodents, then circadian rhythms of behaviour and physiology are lost [16, 17]. Conversely, transplantation of SCN is restorative, supporting the notion that the SCN is a master regulator of circadian rhythms [18, 19]. Thus our cardiovascular physiology exhibits striking time-of-day dependent oscillations regulated by the circadian system.

Daily Rhythms in Cardiac and Cardiomyocyte Function

There are also daily rhythms in cardiac function, and remarkably, these time-of-day variations have been shown to persist experimentally even in the ex vivo setting. For example, isolated perfused rodent hearts exhibit greater cardiac output during the rodent wake time versus sleep period, indicative of greater contractile reserve during this time [20, 21]. This observation is important because it shows that not only the extrinsic environment but also circadian factors intrinsic to the heart are important for maintaining daily cardiac rhythms. These intrinsic rhythms are also observed at the cellular level, as cardiomyocyte sarcomeric myosin heavy chain mRNA [22, 23], MYBP-C, desmin, tropomyosin, troponins I and T [24], and Tcap protein [25], and myosin ATPase Ca2+ activity [24, 26] exhibit time-dependent rhythms over the course of the 24h day and night cycle. Daily variations in ion homeostasis pathway genes and proteins (e.g. Ca2+, K+) have also been described [27-29], suggesting that electrophysiologic properties of the heart also differ markedly over the day and night cycle. Rhythms in cardiac function are also linked with daily variations in cardiac metabolism. That is, there are marked fluctuations in increased energetic demand and substrate availability in the day vs. the night, concurrent with time-of-day oscillations in cardiac metabolism parameters, as has been elegantly described by Young and colleagues [7, 30, 31]. Thus in summary, the functional properties of the heart display rhythmicity that vary depending on the time of day or night, and underlie healthy cardiovascular physiology.

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Molecular Gene and Protein Rhythms in the Heart

The circadian system is regulated by an underlying molecular circadian clock mechanism. This core mechanism consists of oscillating levels of nuclear genes and proteins that keep 24h daily cellular time, and is present in virtually all tissues including the heart [32, 33] (Fig. 1B). For example, there are daily oscillations in core mechanism genes Bmal1, Clock, Cry1/2, Per1/2/3 in rodent hearts, as shown by real time polymerase chain reaction (PCR) [22]. Daily oscillations in cardiac gene expression have also been shown in heart tissue explants, from transgenic Per1-luc rats using a bioluminescence approach [34]. Rhythmic gene expression has also been shown in human heart, for the core circadian clock genes Per1, Per2 and Bmal1, by PCR of left papillary muscle tissue [35].

Importantly, the circadian mechanism drives the expression of not only these core genes, but also many additional output genes over 24h day and night cycles; the heart is genetically a different organ in the day versus the night. We revealed that ~13% of genes in the murine heart are rhythmic in the normal 24h day and night environment, by using Affymetrix microarrays and COSOPT bioinformatics analyses [36]. Moreover, it was shown that ~9% of cardiac genes are rhythmic under circadian (constant dark) conditions, using a microarray approach [37]. Furthermore, it is not only the genome that cycles, indeed there is also daily variation in ~8% of soluble proteins in the heart (the circadian proteome), as was demonstrated using 2-dimensional difference in gel electrophoresis and mass spectrometry [24]. Many of these newly discovered rhythmic genes and proteins map to vital biological processes in the heart, and we are also investigating their applicability as biomarkers of cardiac health and disease [38-40]. Thus in summary, the heart cells possess a circadian clock mechanism which regulates rhythmic expression of a wide variety of output genes and proteins, and these in turn influence the daily processes essential for the structure and function of the heart.

CONSEQUENCES OF CIRCADIAN DISTURBANCES ON THE CARDIOVASCULAR SYSTEM

As described in the previous section, circadian rhythms and their molecular clock mechanism underlie our healthy cardiovascular physiology. However, the role that circadian rhythm disturbance plays in onset and progression of cardiovascular disease has been generally clinically unappreciated. Reports do tend to reiterate a key observation that circadian rhythms are implicated in the timing of onset of adverse cardiovascular events (e.g. myocardial infarction (MI, heart attack) [41, 42], infarct size [43-45], stroke [46], ventricular arrhythmia [47-49], and sudden cardiac death [50, 51]). However, it is only recently that the impact of circadian rhythm disturbance on critical cardiovascular illness has been reported (Fig. 1C). For example, several key recent studies reveal that 1) circadian rhythm disturbances in acute care environments can adversely impact remodeling post-MI. 2) Atypical work schedules (e.g. shift work) disturb our circadian system and increase risk of heart disease and worsen outcomes in workers. 3) Sleep disturbances such as obstructive sleep apnea (OSA) are associated with heart failure, and nocturnal therapy attenuates some of the adverse effects of OSA on the cardiovascular system. Moreover, there is a growing clinical appreciation that targeting circadian biology offers novel therapeutic approaches towards the management of cardiovascular disease, and medicine in general. Below, we review the current knowledge on disturbing circadian rhythms and sleep on critical illness and clinical cardiology.

Myocardial Infarction (MI) and Intensive Care Units

Ischemic heart disease is a leading cause of death worldwide. In spite of medical advances, available therapies have had only limited success in improving long term survival of patients suffering from this disease. MI triggers a temporally coordinated inflammatory response designed to clear the infarct region of cellular debris while
at the same time activating reparative pathways crucial for scar formation [52-56] (Fig. 2). We recently demonstrated experimentally that maintaining circadian rhythms and sleep is crucial for innate inflammatory cell recruitment and for limiting scar formation and ventricular remodeling, in a murine model of MI [26]. Conversely, altering the diurnal environment impairs the healing process leading to increased infarct expansion and worsens outcome; the circadian mechanism plays a direct role, by regulating the inflammatory response in the infarct region [26]. These mechanistic observations shed new understanding on how disturbing endogenous circadian rhythms and sleep in acutely ill patients can worsen outcome. Indeed, it is well documented that the modern intensive care environment disturbs patients’ biological rhythms and sleep, through inadvertent increases in noise, light, and other well-established stimuli [57-59]. Maintaining daily rhythms and sleep is a promising non-pharmaceutical approach to benefit patients post-MI [60, 61]. These observations may also be applicable to cerebrovascular conditions such as ischemic stroke and traumatic brain injury, or any other conditions where inflammation in the first few days is crucial to outcome.

Circadian rhythms co-ordinate inflammatory responses crucial for remodeling post-MI.

Shift Work and Heart Disease

In North America and Europe, ~15-30% of the adult population engage in shift work at some point in their careers [62, 63]. According to the World Health Organization, shift work is an occupational disturbance of our circadian rhythms [64]. Moreover it is associated with heart disease [65-68]. Mechanistically, this may be due in part to atypical sleep and wake schedules which can shift sympathetic and vagal autonomic activity, and daily endocrine, metabolic, autonomic and BP profiles, all of which can impinge on cardiovascular health [69-71]. Conversely, circadian adjustment to shift work by using phototherapy can improve performance and health indices [63, 72]. Numerous epidemiologic studies support this link between shift work and heart disease. For example, an increased incidence of ischemic heart disease was reported in paper mill shift workers in Sweden, and this association is readily detectable within the first two decades of shift work [73]. Moreover, an increased risk for coronary heart disease following exposure to shift work was reported in a cross-sectional survey of participants in north-eastern Germany [74]. Furthermore, atypical work schedules were associated with increased risk of MI, stroke, and coronary events, as was demonstrated in a systematic review and meta-analysis of 34 studies collectively evaluating >2 million people [75]. Progression from mild to severe hypertension has also been reported in Japanese male shift workers [76]. Remarkably, even though millions of people engage in some sort of shift work, little remains known about which atypical work schedules best benefit performance while reducing worker fatigue and adverse cardiovascular health consequences.

Disturbed Circadian Rhythms and Sleep

Sleep is under both circadian and homeostatic control. Recent studies have revealed that mutations in circadian mechanism genes can affect sleep in humans. For example, individuals with familial advanced sleep phase syndrome have a mutation in the circadian gene hPer2, and they tend to sleep very early in the evening and wake in the extreme morning hours [77]. Also, delayed sleep phase syndrome (extreme evening preference) is associated with a polymorphism in the human clock gene Per3 [78]. Polymorphisms in other circadian mechanism genes may also be associated with altered sleep timing [79, 80]. Although the causal relationships between these sleep-related circadian mutations and heart disease have not yet been determined in humans they are worthy of consideration; factors affecting sleep can adversely impact cardiovascular health. Indeed, in today’s society, ~40% of individuals do not achieve the recommended hours of sleep [81, 82], and short or long durations are associated with an increased risk of heart disease [83-86]. Mechanistically, inadequate sleep alters daily rhythms in cardiovascular physiology [87-89]. Moreover, at a molecular level it has been shown experimentally that as little as one night of sleep deprivation directly alters circadian gene expression rhythms in the rodent heart, by microarray analysis [90]. Future investigations are clearly warranted to define the links between the circadian mechanism and sleep, and the translational implications for cardiovascular health and disease.

Obstructive Sleep Apnea and Heart Failure

Obstructive sleep apnea (OSA) is a common respiratory disorder of sleep, and observational studies link OSA with increased risk of cardiovascular disease and heart failure, due in part to the consequent disturbed autonomic and hormonal profiles, as has been well reviewed [91-96]. Indeed, sleep-disordered breathing alone is a risk factor for infarct expansion after acute MI [97]. Night time therapy with continuous positive airway pressure (CPAP) treatment attenuates some of the adverse effects of OSA on the cardiovascular system. For example, patients with severe untreated OSA have a higher incidence of fatal and non-fatal cardiovascular events as compared to OSA patients given CPAP therapy [98]. Indeed, sev-
eral studies report that nocturnal CPAP therapy provides cardiovascular benefits [94, 99-104]. From a molecular circadian perspective, a recent study revealed that OSA impairs daily rhythms in circadian gene expression (hPer1 mRNA) in peripheral blood cells, and CPAP therapy normalizes the impaired gene expression profiles [105]. These studies reinforce the notion that disturbing night time circadian rhythms and sleep significantly impacts the cardiovascular system, and moreover that time-of-day therapies such as nocturnal CPAP therapy can reduce cardiac pathophysiology.

**Disturbed Blood Pressure Rhythms and Cardiovascular Disease**

As mentioned previously, BP exhibits a daily rhythmic profile that surges upon awakening and exhibits a ~10% decrease at night. Importantly, some individuals fail to exhibit the nocturnal dip in BP, so called “nondippers”, and this diminished nocturnal BP profile is predictive of heart disease. For example, a reduced nocturnal BP dip is associated with an increased risk of cardiovascular mortality [106-108]; interestingly, this is observed in both normotensive individuals and hypertensive patients as well [106]. Also, hypertensive nondippers exhibit greater left ventricular cardiac hypertropy, as compared to hypertensive patients with the normal 10% reduction in BP at night, further supporting the notion that loss of nocturnal BP rhythms contributes to cardiovascular pathology [109]. These observations are especially important from a therapeutic perspective because time-of-day therapy (chronotherapy) to restore the nocturnal BP dip profile is effective at reducing cardiovascular-related morbidity and mortality [110-112].

**Timing of Therapies (Chronotherapy) to Benefit Cardiovascular Disease**

There have been several exciting new studies supporting the notion that timing of drug administration may provide significant clinical benefit for patients with heart disease, in addition to improving nocturnal BP as noted above. Many of the World Health Organization essential medicines and many of the best-selling drugs target circadian gene pathways, thus providing a rationale for why therapies may be more effective if given at specific times of day or night [113]. We demonstrated in a preclinical study that administering the short-acting angiotensin converting enzyme inhibitor (ACEi) captopril at sleep time reduced cardiac remodeling in mice with pressure-overload induced cardiac hypertropy; the drug given at wake time had no beneficial effect and was similar to placebo-treated animals [114]. The improved efficacy at sleep time correlated with the diurnal profiles of the renin-angiotensin system targeted by ACEi [114]. Another recent chronotherapy study found that evening administration of aspirin reduces morning platelet reactivity; this has important clinical implications as platelet reactivity contributes to the early morning peak of acute cardiovascular events such as MI [115]. Thus it is postulated that taking aspirin at bedtime instead of on awakening can reduce the incidence of MI during the high risk morning hours. In a similar light, a series of studies by Chan et al., (and others) shows that nocturnal dialysis provides cardiovascular benefit to patients with end-stage renal disease and LV hypertrophy, as compared to conventional day time treatment [59, 116, 117]. We created a blog which summarizes these and other studies on chronotherapy to benefit patients with heart disease (see http://chronobiapp.blogspot.ca/).

**EXPERIMENTAL MODELS OF RHYTHM DISTURBANCE AND HEART DISEASE**

Circadian rhythm disturbances have profound implications for the cardiovascular health of critical care patients, shift workers, individuals with circadian and sleep disorders, or anyone subjected to the 24/7 demands of society. Although the above mentioned studies tend to emphasize the consequences of disturbing circadian rhythms and sleep in the clinical (human) environment, there are also many exciting new studies using rodent models and transgenic approaches to better understand the mechanisms involved. This section will focus on experimental studies investigating the profound adverse effects of circadian rhythm disturbances on the cardiovascular system.

**Circadian Dyssynchrony Causes Dilated Cardiomyopathy**

Circadian organization is a critical factor for cardiovascular health, and chronic dyssynchrony causes dilated cardiomyopathy. This was demonstrated in a study using golden hamsters carrying a mutation in the circadian mechanism gene casein kinase 1 epsilon (CK1ε) [118]. The mutant allele reduces the circadian period from ~24h in the wild type animals (+/+) to ~22h in the heterozygotes (+/−) [18], and also reduces longevity in the heterozygotes [118]. We discovered a causal link between circadian dysregulation and cardiac pathology. That is, the +/− heterozygotes develop dilated cardiomyopathy and severe renal disease when housed in a normal 24h day and night environment that is out of sync with their endogenous 22h circadian period [119]. Conversely, only on light cycles appropriate for their genotype (22h) is the cardio-renal disease prevented [119]. Thus, circadian coordination of daily physiology is critical to the integrity of the cardiovascular system, and maintaining normal circadian rhythms is an important measure for preventing heart disease.

**Disturbing Light and Dark Cycles Exacerbates (Worsens) Cardiac Remodeling**

Chronic circadian desynchronization also has deleterious effects on cardiac remodeling. For example, Penev and colleagues showed that chronic reversal of the light and dark cycle at weekly intervals decreases survivorship of cardiomyopathic hamsters [120]. Furthermore, we showed that altering the daily light and dark cycle from 24h to 20h causes maladaptive cardiac remodeling in mice with pressure-overload induced cardiac hypertropy; the adverse remodeling ceases only when the animals are returned to a 24h environment consistent with their internal circadian rhythm [121]. Light profoundly influences cardiovascular physiology, and as these studies show, disturbing the light and dark cycle exacerbates remodeling in heart disease.

**Circadian Mutations and Heart Disease**

It is only recently that the core circadian genes have been identified, along with sufficient advances in transgenic murine technologies, such that they can be used to directly investigate the causal role of circadian mechanism factors on heart disease. For example, Bmal1-deficient mice develop dilated cardiomyopathy concurrent with altered sarcomeric structure [122]. Interestingly, we recently reported that CLOCK and BMAL1 transcriptionally regulate sarcomeric Titin Cap (Tcap), consistent with the notion that the circadian mechanism is a critical regulator of cardiac sarcomeric structure and function [25]. In another study, mice with simultaneous deletion of three circadian mechanism output genes (Dbp, Hif1α, Tef) develop cardiac hypertrophy and LV dysfunction [123]. Eckle and colleagues reported reduced tolerance of PER2 knockout mice to myocardial ischemia-reperfusion injury [124]. A number of studies have also associated circadian gene mutations with metabolic disturbances [125-127], which is interesting because metabolic disorders such as diabetes, obesity and metabolic syndrome are risk factors for heart disease. Lastly, Young and colleagues have performed sophisticated genetic manipulations in a cardiomyocyte-specific manner to investigate the direct role of the circadian clock mechanism on cardiac pathology. The cardiomyocyte CLOCK-mutant mice (CCM) are predisposed to the development of cardiac hypertrophy [20]. Cardiomyocyte Bmal1-mutant mice (CBK) develop dilated cardiomyopathy [128, 129]. Future studies using transgenic and knockout murine models will undoubtedly provide novel insights into how the clock mechanism regulates vital cardiac processes, and shed new light on our understanding of heart disease.
CONCLUSION AND FUTURE DIRECTIONS

In conclusion, circadian rhythms influence cardiovascular physiology and are vital to good health. Disturbing rhythms and sleep has profound adverse consequences on critical illness and adversely impacts the cardiovascular system. In the future, experimental rodent transgenic models will be used to investigate the full extent by which the circadian mechanism influences cardiac pathophysiology. Significant opportunity also exists to apply circadian biology to other areas of clinical medicine and heart disease, including cardiorespiratory, cardiorenal and/or cerebrovascular conditions. Collectively, these are the major causes of death worldwide, and innovative new strategies to benefit patients are warranted. Considering the importance of circadian rhythms and sleep provides novel approaches to improving the management and treatment of heart disease in clinical settings.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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