Title:
Blood Pressure and Restorative Sleep Intensity are Altered by Chronic Daytime Sleep Disruption in Rats

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ACCEPTED

Session Title:
Rising Stars of Research and Scholarship Invited Student Posters

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Applicable Category:
Academic, Students, Researchers

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cardiovascular, shift-work and sleep

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Abstract Summary:

There is a serious need to develop preventative strategies reducing night-shift workers' risk of cardiovascular disease and stroke. I developed an animal model of disrupted sleep and found when rats had abnormal sleep patterns, overall sleep quality (quantified by delta power in the electroencephalogram) suffered and blood pressure increased significantly.

Content Outline:

1. Introduction
   1. Night-shift schedules may increase the risk for cardiovascular (CV) disease and stroke and shift-workers who sleep irregularly or during the day may experience elevated blood pressure (BP) during sleep. Although clinicians typically use BP data during wake
to assess CV health, BP patterns during sleep may be more informative for determining CV disease risk.

2. Disrupted sleep is an important and overlooked CV disease risk factor for humans but mechanisms by which sleep affects CV health remain incompletely defined, underscoring the need to initiate this research in an animal model. My research aligns with Sigma’s conference theme to “Connect. Collaborate. Catalyze.”, as I am utilizing innovative technology (quantitative electroencephalogram [EEG] characterization to measure depth of sleep and continuous BP monitoring) and a multidisciplinary approach to gain a comprehensive picture of risks associated with disrupted sleep to drive future preventative research and policy change.

2. Our pre-clinical model demonstrates disrupted sleep reduces relative percent power in the EEG delta band and increases BP.

1. When rats could not rest during their preferred sleep period (light/day phase), they failed to compensate for the lost sleep during the dark phase.

   1. The relative % of the power in the EEG delta band is used as an index of the intensity of non-rapid eye movement (NREM) restorative sleep. In sleep-disrupted intervention rats, the relative delta % was decreased during the daytime (9:00-17:00) but did not increase at night to compensate for the restorative sleep loss.

   1. Intervention sleep-disrupted rats (n=5): baseline relative delta (%) light-phase = 24.7 ± 0.25, dark-phase 20.8 ± 0.28 (p<0.01); intervention day 28 relative delta (%) light-phase = 21.8 ± 0.24, dark-phase 20.5 ± 0.3 (p=NS).

   2. Control rats (n=5): baseline relative delta (%) light-phase = 25.3 ± 0.33, night 20.47 ± 0.33 (p<0.01); control day 28 relative delta (%) light-phase = 31.6 ± 0.44, night 24.8 ± 0.41 (p<0.001).

2. Overall time spent in each sleep stage did not change over the study period in intervention or control rats, masking the potential negative physiologic effects of the NREM restorative sleep loss.

   1. Intervention sleep-disrupted rats (n=5): Baseline percent wake 37.16% vs. intervention day 28 percent wake 37.92% (p=NS). Baseline percent NREM sleep 54.14% vs. intervention day 28 NREM sleep 53.1% (p=NS).

   2. Control rats (n=5): Baseline percent wake 42.28% vs. control day 28 percent wake 42.1% (p=NS). Baseline percent NREM sleep 43.48% vs. intervention day 28 NREM sleep 41.06% (p=NS).

2. When rats could not rest during their preferred sleep period (light/day phase), blood pressure increased during wake and sleep.
1. Systolic BP increased during wake and sleep in intervention rats; this BP increase was not reflected in control animals.

   1. Systolic BP during sleep (24-hour mean) in intervention sleep-disrupted rats (n=5): baseline= 124.7 ± 5.17 mmHg vs. intervention day 28= 129.7 ± 5.4 mmHg (p=<0.001).

   2. Systolic BP during wake (24-hour mean) in intervention sleep-disrupted rats (n=5): baseline= 131.6 ± 6.6 mmHg vs. intervention day 28= 139.5 ± 6.5 mmHg (p=<0.001).

   3. Systolic BP during sleep (24-hour mean) in control rats (n=5): baseline= 121.6 ± 6.2 mmHg vs. control day 28= 124.2 ± 5.9 mmHg (p=0.06).

   4. Systolic BP during wake (24-hour mean) in control rats (n=5): baseline= 121.5 ± 7.2 mmHg vs. control day 28= 123.8 ± 6.02 mmHg (p=0.1).

2. Diastolic BP increased during wake in intervention rats; this BP increase was not reflected in control animals

   1. Diastolic BP during wake (24-hour mean) in intervention sleep-disrupted rats (n=5): baseline= 88.8 ± 3 mmHg vs. intervention day 28= 91.7 ± 2.7 mmHg (p=<0.05).

   2. Diastolic BP during wake (24-hour mean) in control rats (n=5): baseline= 86.5 ± 3.5 mmHg vs. control day 28= DBP 87.3 ± 4.8 mmHg (p=NS).

3. Research pairing pre-clinical models with innovative technology increases ability to study mechanisms linking disrupted sleep with increased hypertension and CV risk in shift-workers. This animal model is a necessary first step to develop future translational research, evidence-based practice strategies and health outcome improvement.

   1. Continuous invasive and longitudinal polysomnography in not possible in human studies and current wearable technology used to monitor sleep cannot quantify the precise changes in the EEG power spectral analysis that may be indicative of future CV risk.

      1. In one study, mean absolute percentage error in wearable trackers ranges from 12-32% for total sleep time.

      2. Sleep is complex, influenced by many internal and external factors, and tightly controlled pre-clinical studies are paramount to understand changes in sleep physiology with sleep disruption and the underlying pathways.

   2. Many studies linking BP and future outcomes use in-office daytime BP measures. We show that disrupted sleep is associated with increased BP during NREM sleep, which may be a more informative marker for CV disease and stroke risk.
1. A 10-20% decrease in mean BP during sleep (known as the “BP dipping”) occurs in healthy CV physiology.

2. Bedtime hypertension therapy to achieve reduction in BP while sleeping has been shown to reduce CV events by 61%.

3. Animals with light-phase sleep disruption are not able to achieve physiologic BP dipping with sleep and demonstrate an overall increase in BP during sleep and wake. This poses a feasible strategy to reduce increased risk of chronic hypertension, stroke and CV events if successfully translated to humans.

3. Conclusion

1. Our model represents a powerful tool for determining the mechanisms underlying elevated systolic BP and for testing interventions to protect shift-workers from the CV consequences of poor sleep. Undertaking this challenging health problem is incredibly relevant to the mission of Sigma by advancing global health in the large population of people with disrupted sleep.

2. The research is the necessary first step to produce compelling evidence on the benefit of CV disease prevention in the spectrum of people with disrupted sleep (e.g. shift-workers, military service members, and patients with sleep apnea or insomnia). Future policy decisions in risk prevention for shift-workers may be produced from this line of research.

Topic Selection:

Rising Stars of Research and Scholarship Invited Student Posters (25201)

Abstract Text:

Background/Significance and Purpose: Modern lifestyles do not emphasize the need for healthy sleep. Over 15 million Americans have occupations requiring shift-work, such as nursing, military, and law enforcement. In the Nurses' Health Study (NHS) and NHS II, shift-work was linked to difficulty sleeping, stroke, coronary heart disease, and hypertension. Shift-workers who sleep irregularly or during the day may experience elevated blood pressure (BP) during sleep. Although clinicians typically use BP data during wake to assess CV health, BP patterns during sleep may be more informative for determining CV disease risk. Shift-work leads to recognized disruptions in circadian rhythms and sleep that can exert a deleterious impact on autonomic function and BP. Misalignment of circadian clocks in the brain and peripheral tissues (e.g., CV) lead to metabolic syndrome and endothelial changes in blood vessels. Disrupted sleep is an important—and overlooked—CV disease risk factor for humans. However, the mechanisms by which sleep affects CV health remain incompletely defined, underscoring the need to initiate this research in an animal model.

I used the Two-Process Model of Sleep Regulation to guide my understanding of sleep physiology and the 24-hour sleep/wake cycle. Two processes regulate sleep/wake cycles: (1) Process C (circadian-related) and (2) Process S (sleep-related). Process S is the pressure to sleep, which is dependent on time spent awake since a previous sleep period. Process C is separate and regulated by the suprachiasmatic
nucleus in the hypothalamus, which is the intrinsic circadian clock, and controller of the internal drive to sleep or stay awake. Based on the model, daily patterns of sleep and wakefulness and total sleep propensity result from the interaction among circadian rhythm (Process C) and homeostatic sleep drives (Process S). Sleep outside of the appropriate time in the 24-hour cycle (i.e. during the day in humans where Process C sleep drive is low) is posited to cause metabolic and physiologic disturbances and consequent adverse health outcomes.

The purpose of this study was to test the hypothesis that chronically disrupted sleep decreases overall sleep quality and elevates BP and heart rate (indicators of an over-active sympathetic nervous system) in rats. We also determined whether sleep disruptions modify rats’ endogenous 24-hr rhythms (using core body temperature as a marker of circadian rhythm). This study makes an original contribution to nursing science because the research will advance knowledge about the mechanisms linking sleep disruption with changes in BP and is necessary for future translational research.

**Method:** I developed a rat sleep-disruption model to examine the consequences of disrupted sleep on the CV and neurological systems. In 10 Wistar-Kyoto rats (aged 12 weeks), transmitters were implanted for continuous telemetry monitoring. A catheter implanted in the abdominal aorta was used to measure BP, heart rate and temperature (for Process C). Process S and sleep characteristics were measured by implanting cortical EEG electrodes. This approach has an important advantage because I compared BP and EEG measures during wakefulness and non-REM sleep.

Rats were randomized to an experimental (N = 5, 8-hrs of daily sleep disruption) or control (N = 5, no sleep disruption) condition. Process C was entrained to light (0800-2000) and dark (2000-0800) periods. Rats were undisturbed for 7 days (baseline). On Day 8, a mechanical arm disrupted the ability to rest for 8 hours during the light-phase in the intervention animals (0900-1700). The sleep disruption chamber (Lafayette Neuroscience Sleep Chamber, Indianapolis, IN) is a specialized cage where a mechanical bar sweeps across the cage every 7 seconds to keep the rat awake. The control rats (group 2) were placed in the same sleep disruption cage, but the mechanical arm was be kept off to allow sleep.

EEG/electromyogram (EMG) data was amplified, filtered, and digitized (Ponemah software, Data Sciences International; Minneapolis, MN), and sleep-wake stages were assigned in 10-sec epochs (NeuroScore software, Data Science International, St. Paul, MN). This software applied criteria for discriminating wakefulness (high-frequency, low-amplitude EEG with high EMG tone), non-REM sleep (increased spindle and theta activity with decreased EMG tone), and REM sleep (low ratio of delta/theta activity with low EMG tone). Delta frequency (< 4 Hz) was used to identify the deepest stage of non-REM sleep and measure sleep intensity/quality. Continuous sleep and CV data were aggregated into hourly means. Cosine waves were generated to model 24-hr rhythms in temperature.

**Results:** When rats were exposed to the sleep disruption intervention during their preferred sleep period (light-phase), they failed to compensate for the lost sleep intensity during the dark-phase. Process S sleep disruption did not decrease total non-REM sleep time in intervention rats (baseline= 54.14% vs. intervention day 35= 53.1% [p=NS]) or control rats (baseline= 43.48% vs. control day 35= 41.06% [p=NS]). When sleep was disturbed during the light-phase, however, rats demonstrated a significant reduction in non-REM sleep intensity for the entire 24-hr period. At baseline, the deepest sleep occurred during the light-phase—typical of nocturnal Wistar-Kyoto rats. When sleep was disrupted during the light-phase in intervention animals, the relative power in the delta band was reduced by 21% compared with baseline sleep intensity (p<0.001); this value did not increase during the dark-phase.
when the animal was given the opportunity to sleep (intervention day 35 relative delta [%] light-phase=21.8 ± 0.24, dark-phase 20.5 ± 0.3 [p=NS]). There was no significant change in non-REM sleep time or depth in control rats.

Process C was not altered by interrupted sleep; core body temperature remained entrained to the light/dark schedule rather than the sleep schedule in both groups of rats. Changing the Process S pattern by sleep disruption, altered 24-hr systolic BP patterns, and when rats could not rest during their preferred sleep period, their systolic BP values increased significantly. Disrupted sleep increased systolic BP during wake (baseline= 131.6 ± 6.6 mmHg vs. intervention day 35= 139.5 ± 6.5 mmHg, p<0.001) and sleep (baseline= 124.7 ± 5.17 mmHg vs. intervention day 35= 129.7 ± 5.4 mmHg, p<0.001) in intervention rats. These changes were not reflected in control animals. Diastolic BP increased by 3-mmHg at sleep disruption day 35 in the intervention animals (p<0.05) during wake, which was also not reflected in controls. No significant changes were found in sleep diastolic BP heart rate.

**Conclusions:** Our model represents a powerful tool for determining the mechanisms underlying elevated systolic BP during wake and sleep from sleep disruption and for testing interventions to protect shift-workers from the CV consequences of disrupted sleep. Restorative non-REM sleep was significantly reduced when rats were not able to sleep during their preferred sleep period. Overall time spent in each sleep stage did not change over the study period in intervention or control rats, masking the potential negative physiologic effects of the sleep intensity loss. Similar to rats, human circadian rhythms are entrained to schedules determined by light/dark exposure. When humans are more active at night—and sleeping intermittently during the day—they may require interventions to reduce BP and risk of future CV disease. Our research strategy will be particularly relevant to designing preventative strategies that reduce cardiovascular morbidity in shift-workers, military service members, and patients with sleep apnea or insomnia.