ORIGINAL ARTICLE

Effect of Sleep/Wake Cycle on Autonomic Regulation

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ABSTRACT

Objective: To evaluate the association between irregular sleep/wake cycle in shift workers and autonomic regulation.
Study Design: Cross-sectional, analytical study.
Place and Duration of Study: Dow University Hospital, Karachi, from August to November 2013.
Methodology: All healthcare providers working in rotating shifts making a total (n=104) were included. Instrument was an integrated questionnaire applied to assess autonomic regulation, taken from Kröz *et al*. on scoring criteria, ranging from 18 - 54, where higher rating signifies strong autonomic regulation, indicating a stable Autonomic Nervous System (ANS) and *vice versa*. Participants were interviewed and their response was recorded by the investigator. Influence of sleep misalignment was measured quantitatively to extract index of autonomic activity.
Results: There was a reduced trend in autonomic strength amongst shift workers. The mean score obtained on the Autonomic Scale was 37.8 ± 5.9.
Conclusion: Circadian misalignment has an injurious influence on ANS which might be valuable in controlling autonomic dysfunction that leads to fatal triggers in rotating shift workers.

Key Words: *Autonomic regulation. Melatonin. Shift workers. Photo period. Circadian rhythm. Kröz autonomic scale.*

INTRODUCTION

The body clock regulating the sleep/wake cycle is located in the Suprachiasmatic Nuclei (SCN) of the hypothalamus.[1] Outputs from this internal pacemaker, design oscillation of various physiological rhythms and behaviors through autonomic and/or neuro-humoral activation.[2] The Autonomic Nervous System (ANS) is controlled by a dispersed neural network. Light is a major environmental signal for the SCN, reaches its neurons directly *via* the retino-hypothalamic tract passes through the descending sympathetic tracts and finally innervates nor adrenergic terminals on the pinealocytes. Within the pineal gland, melatonin synthesis is activated at night by the release of norepinephrine from the superior cervical ganglion (Figure 1).

The pre-autonomic neuron committed to pineal gland where diurnal frequency in plasma melatonin pulsation is entrained by a mixture of glutamatergic and GABAergic SCN signals.[3] The dark/light cycle (night/day) maintains the circadian rhythm of sleep *via*, luminous generated light cycle (day) of GABAergic SCN synaptic output to the Para Ventricular Nucleus (PVN) which permits SCN to block glutamergic input from PVN resulting in decreased melatonin concentration during the day (light cycle) and stimulate melatonin synthesis in the pineal gland with a nocturnal peak (dark cycle, Figure 1).[4-6]

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Received: September 01, 2014; Accepted: April 16, 2015.

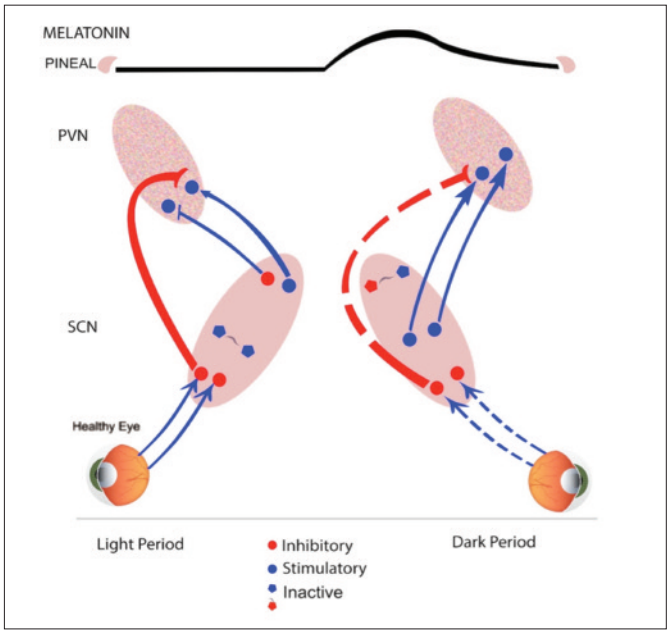

Figure 1: Diagrammatic representation of day/night cycle of GABAergic (inhibitory) and Gutamergic (stimulatory) neurons of SCN regulating ANS and releasing melatonin.

The oscillatory signal of the biological clock is sent to the endocrine and metabolic systems *via* the efferent system from the SCN mutually to neuroendocrine and pre-autonomic neurons in the hypothalamus.[7] Other down stream effector mechanisms are almost certainly involved by this endogenous body clock SCN neuron signaling.[8] The role of one such effect or system is the autonomic nervous system. Heart Rate Variability (HRV) operates according to a circadian rhythm. The lowest HRV is observed in the morning.[9] Apparent circadian variations exist in cardiac arrhythmia, and it has been postulated to be associated with the circadian

expression of ion channels or physiological responses to autonomic nervous function, evidenced by the multi-synaptic autonomic connection from SCN neurons to the heart.[10] The shortcoming of this extremely unified system, becomes obvious when our daily routines are not aligned with the environment.

Nurses and other healthcare providers have to be accessible to patients around the clock which is only possible through shift work. As a result, there is a misalignment of endogenous rhythm and social sleep-wake timing. When the sleep/wake oscillatory process is not synchronized, as in shift work, there is an increased risk of developing cardiovascular, metabolic, and gastrointestinal, disorders, some types of malignancies and burn-out.

The aim of this study was to evaluate the effect of misaligned sleep cycle and autonomic dysfunction from the circadian rhythm perspective and subsequently to find out whether miscommunicated dark/light cycle to the biological clock has autonomic effect in irregular shift workers.

METHODOLOGY

This cross-sectional study was carried out at Dow University Hospital, Karachi, from August to November 2013. Subjects included entire population of healthcare providers (n=104) working in rotating hour shifts (defined as irregular shift). Initially 10 healthcare providers were examined by the measuring tool (integrated questionnaire) to assess the data gathering process. Written and informed consent was obtained from all participants. Sociodemographic characteristic of the subjects included age, gender, marital status and education. Subjects with history of chronic morbidity, nicotine use, caffeine intake and any drug abuse were excluded. A formal ethical approval for this non-interventional study was not required by the institution, although, it fulfilled contemporary ethical standards. However, a formal written permission from the hospital management was obtained.

Investigator recorded the response of each participant by means of integrated questionnaire tool by Kröz *et al*.[11] Screening instrument (questionnaire) employed to find out autonomic regulation incorporated eighteen-item total score with three different functional units. Feature number 1 included orthostatic-circulatory balance, feature number 2 included rest/action control and feature number 3 was based on digestive regulation, questions related to the chemistry of autonomic functions such as rest/activity sequences, vertigo, orthostatic parameter, heat adjustment, energy metabolism along with added questions intended to verify self-reported sleep period and quality, as well as day-time functioning which could reflect the rest/activity rhythm. This screening international tool is designed on a set of scoring criteria to assess physical symptoms related to autonomic function on a measuring scale having a range from 18 to 54 (answer scale from 1 - 3) where high rating signifies strong autonomic regulation and low rating suggests a weak autonomic regulation.

All data analysis was carried out on SPSS version 20 for windows. Quantitative variables were presented by mean and SD values; the qualitative variables were presented by frequency and percentages. Chi-square test was applied at 5% level to find out association of age, sub-groups, gender, marital status, and length of job with autonomic regulation. Results were considered significant at $p < 0.05$.

RESULTS

One hundred and twenty rotating shift workers were invited to participate in this study. Nine subjects did not complete the interview and 7 individuals declined to participate. We had complete data from 104 participants. Response rate was 87% (n=104, Table I). The age ranged from 19 to 56 years. Mean score obtained on autonomic strength scale was 37·8 ± 5·9 (Figure 2). More than half of the participants were males (Table I). The subjects were healthcare provider working in shifts.

Table I: Demographic features of study population (n=104).

Variables	N	(%)	Mean ± S.D
Age (years)			28.3 ± 6.0
Gender			
Male	63	60.6	
Female	41	39.4	
Overall score			37.8 ± 5.9
Nurses	66	63.5	
Technician	30	28.8	
Assistant nurses	8	7.7	
Nurses score			37.9 ± 6.2
Technician's score			38.2 ± 5.4
Assistant nurses score			35.9 ± 5.8

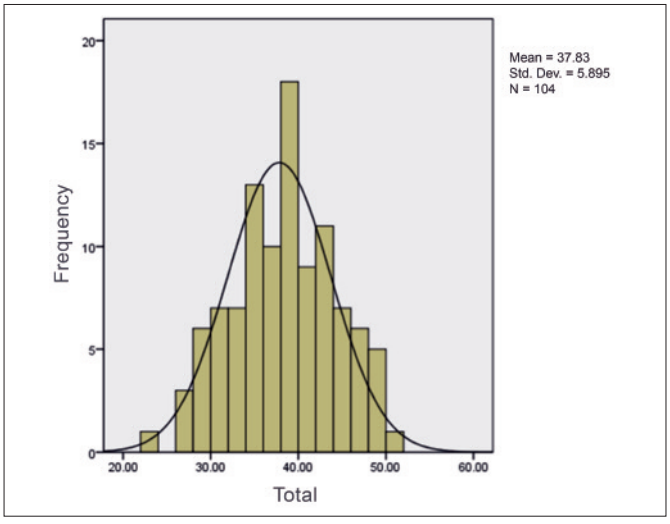

Figure 2: Graphical representation of mean score (shift worker) obtained on autonomic scale.

Sub-groups, based on the education and job description, included nurses, technicians and assistant nurses. Mean score attained by nurses was 37·8 ± 5.9; technicians scored 38·2 ± 5·4 and nurse assistants scored 35·9 ± 5·8 on the measuring scale.

Since the screening tool had 18 items, lowest response (answers) on this scale was 18 and highest was 54. To find out autonomic strength, the responses were divided into three categories of low group < 36, moderate group (37 - 40) and high group (> 41). Majority of the subject (n=41) scored below < 36. Other groups included 30 and 33 subjects respectively. Chi-square test was applied to determine association of age, sub-groups, gender, marital status and length of job with autonomic strength results were considered significant at $p < 0.05$. The results did not reveal any significant difference between gender and autonomic strength (p=0.135). However, significant difference was observed between autonomic strength and age (p=0·017). Based on job tenure, two sets were formed; the first group had been in this profession for less than 2 years and second group for more than 2 years. There were no significant difference between the two groups for autonomic strength (p=0·689). Fifty nine (56.7%) of the subjects were unmarried and 45 (43·3%) subjects were married (p=0.421).

DISCUSSION

The findings supported the initial hypothesis that irregular sleep/wake cycle has a negative impact on autonomic strength. Results reflected reduced autonomic regulation (mean score = 37.8 ± 5.9 for a maximum of 54).

Proximate research revealed that individual neurons from the SCN, when dissociated and held *in vitro*, preserve a vigorous circadian rhythm in electrical firing. The circadian rhythmicity is parallel in both electrical and metabolic pathways. However, current study focused exclusively on electrical activity. The suprachiasmatic nucleus was considered a source of autonomic dysfunction in rotatory shift-workers. Nurses, because of their nature of job, remain committed to performing important and difficult work. Irregular working hours can cause a decline in abilities, somatic and psychological ailments, and increase in human error.[12,13] Current results did not show autonomic failure however, results demonstrated reduced autonomic regulation that might explain how these shift workers were still able to cope with their job requirement. Their job tenure might be another factor which guards them from major autonomic derangement. It was observed that participants in the current study had been in this profession for a maximum of 6 years. The arrangement of the autonomic nervous system in the primitive neural circuit also probably provide an adaptive response in maintaining the autonomic function to a desirable level in these workers.[14]

Since the time-keeping system of the body involves the Central Nervous System (CNS) as well as the ANS, research was focused on the complex relationship between circadian rhythmicity of sympathetic and parasympathetic nervous activity and Heart Rate Variation (HRV). Consequently, the research community focused on HRV as a valuable tool to investigate sympathetic and parasympathetic functions.[15] However, HRV alone is a poor index of ANS regulation. Hence the two branches of the ANS can perform in a reciprocal fashion co-activated or co-inhibited, or operate uncoupled.[16,17] The probable contribution of the autonomic function in health and disease was first reported by Rudolf Steiner in the 1920s. This research has not only focused on autonomic regulation of heart to assess autonomic function, but has also presented a model to appraise the course of ANS dysfunction originating predominantly from pineal melatonin system all the way down to the effector systems in human beings. This tool has incorporated the assessment on self-reported autonomic strength by measuring sleep schedule, vertigo, bowel habits, thermoregulation, rest and activity metabolism.

The distinct label of ANS dysfunction is linked with a multitude of complex, disorders and diseases with diverse pathology, such as diabetic autonomic neuropathy, hyperhidrosis, orthostatic intolerance/ postural tachycardia syndrome, pure autonomic failure, and vasovagal syncope.[18,19] Shift work disturbs sleep and natural biological rhythms in humans, which might increase psychosocial stress and predispose the individual to physiological disturbances related to the metabolic syndrome.[20,21]

Previous studies have addressed a variety of diseases associated with shift work, including gastrointestinal (GI) symptoms. One study observed that shift-work affected the intestinal peristalsis and resulted in disordered digestive enzymes and acid-alkaline balance. These disorders might be related to sleep pattern, as they had a correlation with the previous night's sleep quality in these subjects.[22]

In another research, prevalence of peptic ulcer disease was higher in shift-workers (2.38%) than in day workers (1.03%). Duodenal ulcer was also found to have greater prevalence in shift workers as compared to day workers (1·37% and 0·69%, respectively).[23] Other research in Iceland revealed that nurses employed for 16 hours in a morning-evening shift had more severe GI problems.[24] A proximate research of chronic insomniacs observed that stimulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis in this population resulted in elevated sympathetic tone and raised cortisol levels. Stimulation of the HPA may be attributed in part to Corticotrophin-Releasing Hormone (CRH), and this neuropeptide may represent a significant link between ANS and CNS activation in insomnia.[25]

This study conceptualized both psychosomatic functions and somatic functional loss below the level of consciousness. Functionally, when the environment is synchronized with the internal biological clock, bodily state is regulated in an efficient manner e.g., visceral homeostasis. Present research had focused on life style as a major factor responsible for autonomic dysfunction. In the last few decades, there have been major changes in life style especially due to television, additionally many workers such as students with part time jobs, work in places like night stores and video-game shops that remain open 24 hours, all of which seems to misalign circadian oscillation and create distress for the ANS. Previous studies revealed that autonomic strength was influenced by age and gender and it was observed that younger subjects performed better on the autonomic rating. This trend remained constant in this study and there was a significant association between age and autonomic regulation. However, no association could be established between gender and autonomic regulation.

CONCLUSION

The current study has demonstrated pineal melatonin time keeping oscillation (sleep cycle) hold a injurious influence on autonomic strength. This approach might be particularly helpful when treating underlying autonomic pathophysiology.

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