*Original Article*

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# Association of salivary cortisol with chronomics of 24 hours ambulatory blood pressure/heart rate among night shift workers

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Summary

**Recent studies indicate a circadian rhythm in blood pressure and heart rate and its association with various neurotransmitters. In the present study, we examine the circadian nature of blood pressure/heart rate and salivary cortisol in night shift workers and whether these circadian changes produced by night shifts are reversible. Sixteen healthy nurses of both genders, aged 20-40 years, performing day and night shift duties, were randomly selected out of 22 who volunteered for this study. Ambulatory blood pressure monitoring was done in all the subjects and salivary cortisol levels were analyzed during both day and night shift duties. There were clinically significant changes in the Acrophase of blood pressure and cortisol levels, indicating ecphasia (odd timing of systolic blood pressure) individually during night as well as day shifts. However, this pattern was statistically not significant. A reverse pattern of Acrophase was observed in 8 out of 16 subjects when they were posted on day shift. No significant change was found in midline estimating statistics of rhythm (MESOR) of blood pressure values. Changes in Double amplitude (Predictable change) were observed in 8 subjects during night shifts as well as in 7 subjects during day shifts. However, the pattern was not similar and night workers had an altered circadian pattern in the night as well as during day shifts. Changes in Double amplitude, Acrophase and Salivary cortisol were found during night as well as day shifts but these changes were not statistically significant (*p* > 0.05) due to incomplete recovery during day shifts (changes again seen when they came back to day shifts). Salivary cortisol levels were lowest in early morning, increased at midnight and further increased in the afternoon during night shifts along with ecphasia. It is possible that nurses working the night shift felt more tired due to the altered circadian cycle.**

***Keywords:*** Rotating night shift, ambulatory blood pressure and heart rate monitoring, circadian cycle, ecphasia

## 1. Introduction

Night shift working may be associated with disruption of circadian rhythm, where a person's internal body clock is in swing with the shift schedule. The circadian rhythm of our body is characterized with an alternating cycle of sleep and awakening (*1*). Among healthy subjects, sleep tends to occur during a particular phase of the circadian cycle (*2*). Those who work during the night shift may attempt to sleep when their body clock is adjusted for the awakening phase (*3*). This attempt disturbs the body clock resulting in a contradictory relationship between sleep time and circadian schedule. There is evidence that shift work affects both sleep and awakening by disrupting circadian regulation which has adverse effects on family and societal life (*4*). The

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night shift work alters both length and quality of sleep. Day sleep is light, fragmented, and more likely to be disrupted and hence, insomnia can be severe in night shift workers (*5*). It is possible that circadian sleep propensity rhythm and hormonal rhythm are under influence of the circadian pacemaker as well as sleep habits (*6*).

Most rhythms are driven by an internal biological clock located in the hypothalamic suprachiasmatic nucleus and can be synchronized by external signals such as light-dark cycles (*7*). The rapidly rotating shift system including two consecutive night shifts, do not significantly alter the normal circadian rhythm of the body, particularly performance level, body temperature and hormone release (*8*).

The majority of the circadian rhythms in our body have both an endogenous component regulated by internal clock, Suprachiasmatic nuclei (SCN), and an exogenous component composed of a light-dark cycle (*1,5*). The disruption in the natural time pattern, under influence of a light-dark cycle, acts upon the circadian system to bring it into synchronization with the new time pattern. The circadian blood pressure variation is determined largely by the sleep and awakening cycle under influence of the internal body clock (*9*). Cortisol, a reliable indicator of stress, displays pronounced variation across the time-of-the day with high levels in the morning and low around midnight (*10*). Stress may alter intensity of secretion of cortisol and circadian pattern of the hormone. It is known that a long term increase of circulating cortisol or changes in the circadian rhythm of the hormone enhances the risk of metabolic and cardiovascular diseases including cancer, diabetes and depression (*11*). Identical heart rates and blood pressures have been observed among nurses working night shifts (*12*).

In the present study, we evaluated the circadian nature of blood pressure, heart rate and salivary cortisol in night shift workers, to find out if there is a relationship between circadian rhythm of blood pressure, heart rate and salivary cortisol levels and whether these changes are reversible after change in duty schedules.

## 2. Methods

### 2.1. *Subjects*

Out of 22 volunteers, 6 were excluded due to non-fulfillment of study protocol. The duration and pattern of shift work were the same among all the subjects. Sixteen healthy Healthy nursing professionals (Table 1), aged 20-40 years, performing day and night shift duties (continuous 9 days night shifts with alternate day shifts) for 8 years were willing for compliance to be randomly selected and recruited from Trauma Center, GM and Associated Hospitals, Chhatrapati Shahuji Maharaj Medical University, Lucknow, UP, India. The study was conducted from March to July, 2009 when the average temperature of the city ranged between 34°C and 38°C. At 26.50 N°, Lucknow is located just north of the tropic of cancer. All subjects were working in centralized air-conditioned wards. The study was approved by the institutional ethics committee (*Ref.* code: XXXIV ECM/B-P3) and written, informed consent was obtained from all subjects participating in the study. Healthy nursing professionals of both genders, aged between 20-40 years who performed night and day duty were included in this study. Subjects with any acute/chronic illness, known patients with diabetes mellitus, other endocrinal disorders, hypertension, coronary artery disease, and chronic renal diseases were excluded from this study.

**Table 1. Height, weight and age distribution of male and female night shift workers**

| Baseline characteristics | Male (*n* = 8) | Female (*n* = 8) |
|---|---|---|
| Age | 22.25 ± 1.28 | 26.50 ± 5.80 |
| Weight (kg) | 58.50 ± 10.53 | 50.12 ± 6.66 |
| Height (cm) | 164.50 ± 8.12 | 152.37 ± 3.38 |
| Body mass index (BMI) | 21.63 ± 3.80 | 21.61 ± 2.96 |

Data are presented as means ± S.D. *n*, number of subjects.

### 2.2. *Twenty-four-hour ambulatory blood pressure and heart rate monitoring*

Blood pressure and heart rate were recorded by an ambulatory blood pressure monitor TM-2430 (A & D, Tokyo, Japan) that can measure repeated oscillatory blood pressure and heart rate at desired intervals. Taking serial measurements a few times each day is important to reduce error associated with single measurement. The chronobiologic characterization of the circadian amplitude and Acrophase in addition to the midline estimating statistics of rhythm (MESOR) further reduces the error. Taking only one or two measurements a day, always at awakening and/or at bedtime may fail to reveal abnormalities seen only at other times of the day, or abnormalities that apply only to the variability in blood pressure or heart rate (*13*).

In this study, the subjects wore an ambulatory blood pressure monitor TM-2430 programmed to automatically measure blood pressure and heart rate at 30 min intervals while awake and sleeping hours during night shifts and again when they were shifted to day duties. The data were downloaded after every monitoring span to a local PC *via* an interface (TM-2421, A & D). Each blood pressure and heart rate profile was analyzed by a sphygmochron, utilizing both a parametric and non-parametric approach. Ambulatory blood pressure monitoring records were sent to Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA for further interpretation. Original oscillometric data from each blood pressure series was first synchronized according to the rest activity cycle of each individual by recomputing all the records in hours, from bedtime to avoid differences among subjects in actual time of daily activity and to express results in circadian time rather than in less meaningful clock hours. After synchronization, blood pressure and heart rate values were edited according to commonly used criteria for the removal of outliers and measurement errors. The remaining data were analyzed chronobiologically.

The study of human chronomes can serve the derivation of refined reference values to better define health and to identify pre-disease, so that prophylactic intervention can be instituted as early as possible, preferably before disease sets in (*14*). In the current implementation of the chronobiological recommendations, reference values have been specified for clinically healthy peers of a given gender and ethnicity in different age groups (*15*). Ambulatory blood pressure monitoring was done during their day and night shifts. Some essential parameters which are directly under the influence of night shift work such as body temperature, time of arousal, time of going to bed, duration of nocturnal and diurnal sleep, mode of waking up, sleep latency, quality of sleep, feeding habits, menstrual history (for females), and family history were also recorded. Acrophase (hr:min, Time of overall high/peak values, and Hyperbaric index) were calculated for Systolic blood pressure (SBP), Diastolic blood pressure (DBP), and Heart rate. The circadian amplitude, a measure of the extent of reproducible variability within a day, was obtained by linear curve fitting, which yields added parameters: in midline-estimating statistics of rhythm, the MESOR (a time structure or chronome-adjusted mean), Acrophase (the timing of overall high values), recurring in each cycle, and the amplitude and Acrophase of the 12 hour (and higher order) harmonics of the circadian variation that with the characteristics of the fundamental 24 hour component, describe the circadian wave form. The MESOR is a more precise and more accurate estimate of location than the arithmetic mean (*15*).

### 2.3. *Estimation of circadian pattern of salivary cortisol levels*

Saliva samples were also collected at the time of ambulatory blood pressure monitoring. We collected saliva samples at approx. eight hours intervals in their night shift schedule (afternoon sample: 13:00 to 15:00, night samples between 22:00 to 01:00 and morning samples between 05:00 to 08:00) and during their day shift, 1st sample was taken between 14:00 to 15:00, 2nd at 21:00 to 22:00, and the last sample around 05:00 to 06:00 hours. The volunteers themselves collected the samples in different colored vials. For collection of saliva samples, a notebook was provided to each subject with all details regarding the timing and procedure for sampling and their sleep-wake timing. A thermometer was also given for recording of the circadian pattern of body temp. Each participant was instructed to wash their hands properly before taking the samples and to rinse their mouth with water to remove food particles, if they had taken their meals. They were asked to refrain from eating or drinking anything for at least 30 min after awakening. Saliva samples were then centrifuged at 3,000 rpm for 15 min. Cortisol samples were analyzed by the ELISA method. Salivary cortisol was estimated due to its stability in saliva for a longer time period and its ease of taking for circadian studies. The salivary cortisol concentration was synchronous with the serum concentration, indicating that the salivary assay could be substituted for the serum assay to assess circulatory rhythmicity across the 24-h time frame. Salivary cortisol appears to represent serum cortisol across the 24 h period, except for those on oral contraceptives (*16*). The more pronounced cortisol responses in saliva than in serum and its closer correlation with adreno-corticotropic hormone offer advantages over serum cortisol suggesting salivary cortisol measurement may be used as an alternative parameter in dynamic endocrine tests (*17*).

## 3. Results

As shown in Table 2, blood pressure and heart rate increased during the night and decreased in the early morning during night shift work. Alteration in mean Acrophase (time of overall peak value) of SBP in individual subjects during night shifts was observed, showing ecphasia (odd time of SBP, not of DBP and heart rate). The day shift was associated with a typical circadian rhythm with a drop in both SBP and DBP at night. This pattern was reversed in night shifts. Acrophase was found to be altered in 15 out of 16 subjects when they were working night shifts. This indicated that ecphasia (odd timing of blood pressure) was found in 15 subjects during night shifts. A reverse pattern of Acrophase was found in 8 subjects out of 16 when they were posted on day shifts. Chronobiological studies need to analyze the data individually not statistically. Changes in double amplitude, acrophase, and cortisol levels were significant clinically but these changes did not reach statistical significance due to incomplete recovery when subjects came back to day shifts.

Changes in double amplitude, Acrophase, and salivary cortisol were found during night as well as day shifts but those changes were not statistically significant ($p > 0.05$) due to incomplete recovery during day shifts (changes again seen when they come back to day shifts). No significant change was observed in MESOR. Alterations in MESOR values were observed in 2 subjects during night shifts and these altered patterns were reversed when they were changed to day

**Table 2. Anti-HBV response of TCM and related active compounds in clinical trials**

| Parameters | During night shift | During day shift | *p* values |
|---|---|---|---|
| MESOR | | | |
| SBP | 114.46 ± 9.32 | 113.31 ± 9.23 | 0.30 |
| DBP | 71.28 ± 6.73 | 70.42 ± 5.96 | 0.34 |
| HR | 73.87 ± 3.83 | 73.77 ± 4.04 | 0.46 |
| Double amplitude | | | |
| SBP | 22.48 ± 13.57 | 25.91 ± 13.36 | 0.25 |
| DBP | 17.55 ± 8.90 | 20.29 ± 8.66 | 0.15 |
| HR | 13.31 ± 7.57 | 15.80 ± 10.27 | 0.23 |
| Salivary cortisol levels | | | |
| Evening | 2.73 ± 1.90 | 3.03 ± 2.05 | 0.33 |
| Night | 3.34 ± 3.36 | 2.27 ± 1.95 | 0.13 |
| Morning | 3.46 ± 2.90 | 4.65 ± 2.83 | 0.09 |

Data are presented as means ± S.D.; Abbreviations: MESOR, midline estimating statistics of rhythm; SBP, systolic blood pressure; DBP, diastolic blood pressure.

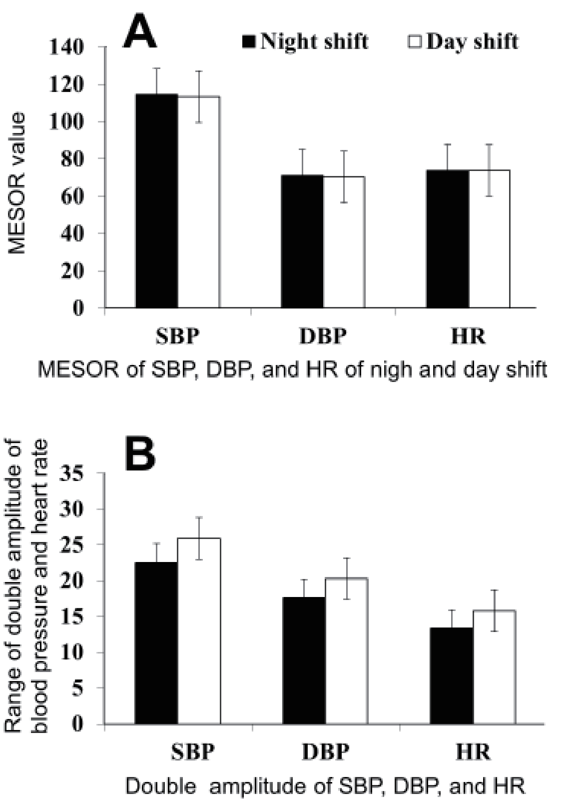


**Figure 1. MESOR and Double amplitude of SBP, DBP, and Heart rate during night and dayshifts. (A)** MESOR of night and day shifts. **(B)** Double amplitude of night and day shifts. Closed column, night shift; open column, day shift. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

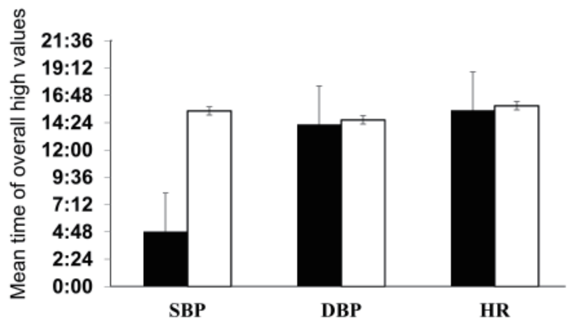


**Figure 2. Acrophase (time of overall peak values) of SBP, DBP, and heart rate during night and day shifts.** Closed column, night shift; open column, day shift. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

shifts. Therefore, MESOR values were normal during day as well as during night shifts (Figure 1A). Changes in double amplitude were observed in 8 subjects during night shifts. While during day shifts, these changes were observed in 7 subjects only, but these patterns were not similar to that found during night shifts. A change in the pattern of double amplitude of SBP, DBP, and heart rate develops later on, 4-6 days after day shifts (Figure 1B).

Alteration in mean Acrophase (time of overall peak value) of SBP during night shifts was observed, showing ecphasia (odd time of SBP not of DBP and heart rate), which was reversed during day shifts (Figure 2). Significant changes were observed in Acrophase, showing ecphasia which may be a clinically significant cause of drowsiness, fatigue, and sleep disturbances in night shift workers. Hyperbaric index is the threshold or upper limit of the tolerance interval. It is a 3-h fractionated time interval. Alteration in circadian pattern of the hyperbaric index was observed during night shift due to an altered sleep-wake pattern, however, in day shift 3 subjects showed a reverse pattern (normal pattern) represented by NC (no change from reference range) which has been shown in Figure 3.

Salivary cortisol levels were decreased in early morning (in 5 subjects), increased at midnight (in 8 subjects) and were highest in the afternoon (in 8 subjects) during night shifts along with ecphasia (odd timing of blood pressure), while during day shifts the altered circadian pattern of cortisol was found to be different in subjects having a normal circadian pattern during night shifts (Figure 4). The normal circadian pattern of cortisol showed diurnal variation and decreased at night with an increase during early

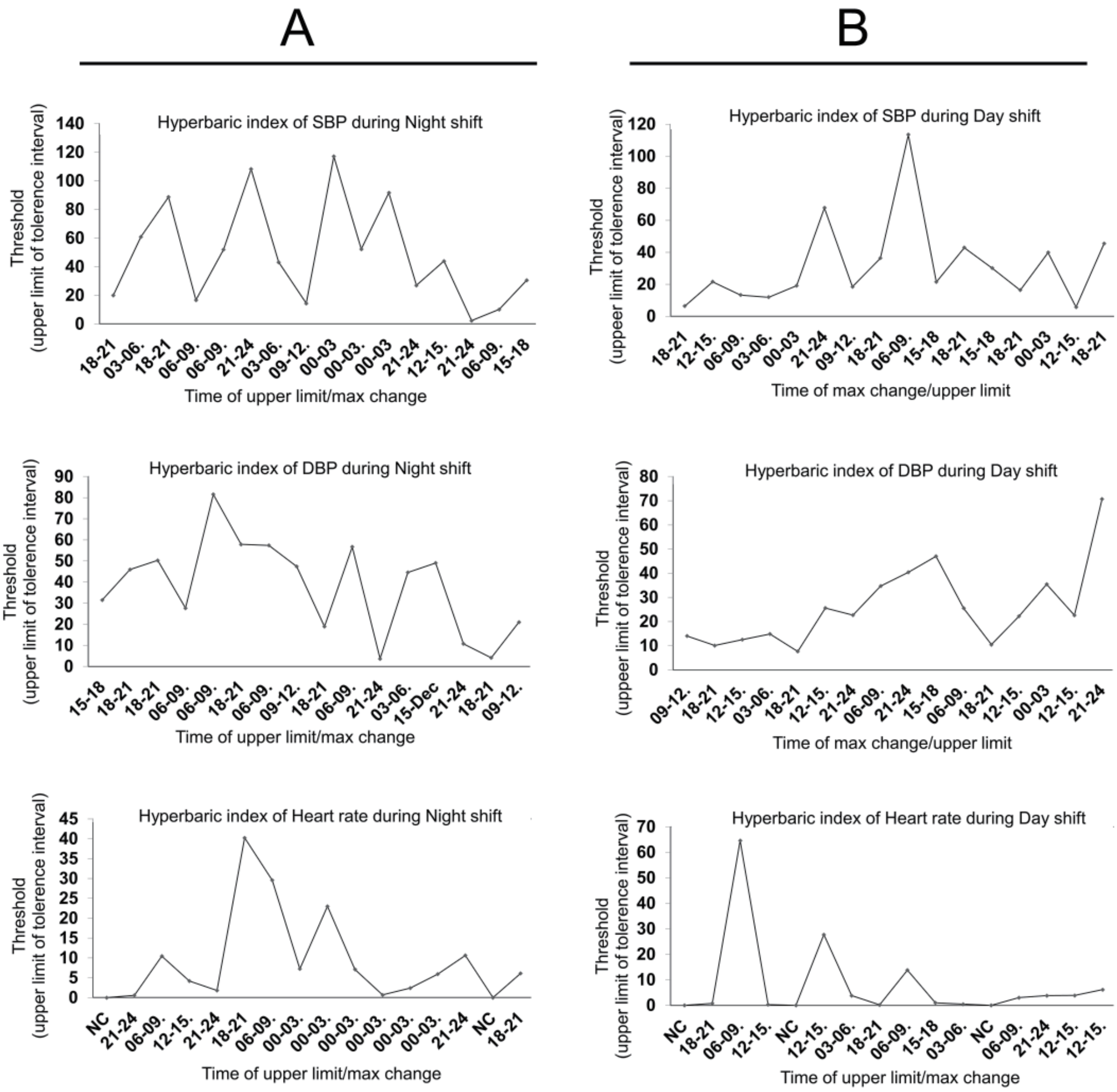


**Figure 3. Hyperbaric Index of SBP, DBP, and Heart rate during night and day shifts. (A)** Night shift. **(B)** Day shift. X-axis represents three hours fractionated time interval at which the maximum change found in a 24 h period. NC means no change from reference range. Y-axis represents threshold or upper limit of tolerance interval in a 24 h period.

morning. Evening cortisol levels during night shifts was normal, however; during day shifts, it showed a slight increase which suggests that the alteration in circadian pattern develops later when shifts were rotated. Night cortisol levels during night shifts were increased and a slightlyreversed pattern was found during day shifts which was not significantly reversed (Figure 5). Morning cortisol levels also showed a slightly reversed pattern during day shifts.

## 4. Discussion

Night shift workers are awake when they are supposed to sleep and attempt to sleep in day time when they are normally supposed to be awake. They have a higher incidence of poorer sleep and its complications (*18-20*). This study shows that the majority of subjects complained of headache, drowsiness, fatigue, and inadequate or poor quality of sleep because of difficulty in falling asleep and maintaining sleep. Our study shows an alteration in circadian pattern of Acrophase and double amplitude of blood pressure and heart rate during night as well as day shifts, which indicates, the phenomenon of desynchronization instead of resynchronization when they are reversed in day shifts. Changes in Acrophase (time of overall peak value) of SBP shows ecphasia (odd timing of SBP) during night shifts and this pattern was reversed during day shifts. A few studies have demonstrated that shift work is associated with increased cardiovascular morbidity and mortality (*21-23*). Alterations in Acrophase and double amplitude showed the predictive cardiovascular disorder. Increased frequency of blood pressure variations, in addition to high blood pressure, has been

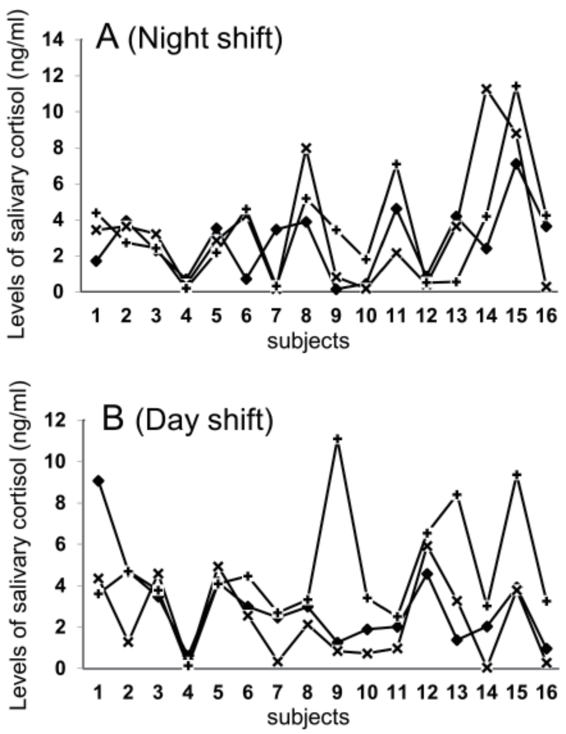


**Figure 4. Circadian pattern of salivary cortisol levels during night and day shifts. (A)** Night shift. **(B)** Day shift. ×, Night cortisol levels; +, morning cortisol levels; ♦, evening cortisol levels.

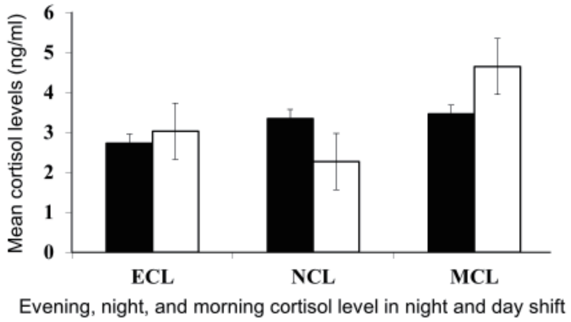


**Figure 5. Circadian pattern of mean salivary cortisol levels during night and day shifts.** ECL, evening cortisol level; NCL, night cortisol level; MCL, morning cortisol level. Closed column, night shift; open column, day shift.

associated with greater target organ damage and higher incidence of cardiovascular events.

The most important physiological mechanisms regarding shift work, particularly night shift work, is the problem of entrainment (resynchronization) of physiological functions after a phase shift of working and sleeping times (*19*). The internal desynchronization of circadian rhythm in physiological rhythms like oral temperature and grip strength are in favor of the hypothesis of an internal desynchronization and clinical intolerance to shift work (*20*). Physical activity is one of the determinants of Ambulatory blood pressure and diurnal variation (*24,25*).

Salivary cortisol appears to be an excellent measure for monitoring circadian rhythm variation in adrenal activity in healthy individuals during shift work (*26*). Higher salivary cortisol during morning and night shifts and the worst quality of sleep in engineers working very fast backward-rotating shifts may be an indication for insufficient recovery (*27*). A reversal of circadian function could be observed for the total group (mean cortisol concentrations) after the fifth night. They exhibited lower duration of less consistency in recovery of sleep across the following days after night work (*28*). The circadian patterns of cortisol during night shift were altered in the afternoon, night and morning phase from that of the normal pattern. The higher salivary cortisol in evening and night hours during night shifts and worse quality of sleep may be an indication for insufficient recovery. The circadian pattern of blood pressure (Acrophase) and cortisol showed a definite correlation in night shift workers. This altered circadian pattern of salivary cortisol appears to be important because it is cortisol which augments various regulatory mechanisms involved with cardio-respiratory regulation including blood pressure and heart rate.

In conclusion, night shift workers appear to have an altered circadian pattern of Acrophase and a double amplitude of blood pressure and heart rate during night as well as during day shifts. These altered circadian changes persisted in most cases even when they were on day shift. However, alteration in cortisol level was observed during night shifts and that cortisol pattern was reversed slightly during day shifts. A larger study would be necessary to confirm these findings. The majority of the nurses working night shifts felt more tired after work due to an altered circadian pattern which indicates that fatigue can negatively influence health, quality of performance, safety and thus, patient care. A chronobiologically interlinked shift design may be important for normal physiological functioning of such professionals to avoid complications of awakening in the night.


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