Bifurcated sleep in night shift workers alters circadian relationships in cardiovascular and temperature rhythms

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Abstract

Shift workers are faced with sleep deficits and circadian disruption, a risk factor for hypertension. We recorded daily rhythms of body temperature and blood pressure (BP) of 28 healthy healthcare workers using thermometers and ambulatory BP monitors, respectively. Participants worked in in regular day (D) shift, regular night (N) shift or rotational shift (RS, i.e., RD/RN during day/night shift) work routines. Different shift regimes had variable effects on sleep quality and duration, thus affecting the waveform of daily BP/temperature rhythms. Therefore, this study aimed to assess circadian misalignment of BP/temperature rhythms under shift-work regimes. In D, 8-h night sleep and robust bimodal rhythmic patterns in SBP, DBP and temperature were observed. Among shift workers, N exhibited bifurcated sleep with long work-hour naps commensurate to the daily peak and dip in BP/temperature. The amplitude of the daily rhythm of BP and temperature was dampened in RS. Overall, cardiovascular rhythm disruption was greater in SBP than in DBP. RS exhibited higher temperatures throughout day-night shifts. Sleep bifurcation, although it immediately recompenses sleep deficits, may be associated with altered circadian waveforms of physiological rhythms, rendering long-term health consequences.

Summary Table-

What is known about topic	**A thermoregulated dip gates sleep preparation, and a nocturnal dip in blood pressure occurs in mid of sleep, resulting in circadian rhythms in body temperature and cardiovascular functions.**
What this study adds	A worktime nap in night workers improves sleep satisfaction irrespective of its duration. Rotational shift work dampens amplitude of body temperature rhythm.
	Sleep bifurcation improves tolerance for night shift work but not the circadian rhythm misalignment.
	It is important to look for avenues critical to human health that contribute to circadian rhythm resynchronization.

Introduction

Shift work predisposes humans to cardiovascular risk factors through circadian disruption[1]. Night shift work not only changes the phase of circadian pacemakers but also leads to observable sleep deficits[2,3]. Temporal adjustments to shift work have been shown to improve through sleep fragmentation, which renders short-term benefit to cope with sleep deficits[4]. In the long term, however, the health consequences of shift work tend to worsen due to (1) repeatedly compromising homeostatic stability and misaligned biological clock, (2) recurring phase re-adjustments, and (3) major rhythm disruption during day(s)-off wherein family needs/social obligations also play a role. A ‘day off’ usually reschedules the shift worker to revert to a night sleep, adding difficulty in transitioning to day sleep. Therefore, an alteration in the

waveform of the daily rhythm of physiological parameters associated with sleep and other bodily functions accompanies the phase change of circadian pacemakers.

Healthcare professionals in hospitals, i.e., doctors, nurses and emergency assistants, ensure timely assistance to desperate and needy patients. These personnel work in different routines, depending on 24/7 alerts due to patient-centred care. These routines include either fixed (day [D] working or night [N] working) or rotational shift work, RS. Rotational shift work is a scheduling system in which employees alternate between day (RD) and night (RN) shifts fortnightly.

The rhythms in bodily functions such as body temperature and cardiovascular (CV) function are directly confounded by the length and quality of sleep[3]. These physiological rhythms are subtle outputs of complex biochemical pathways and cellular events temporally contrived by sleep-wake, food intake or social stimuli, and they operate through the body's regulatory networks. The myriad of constituent pathways and underlying biological networks contribute to differences in the rhythmic nature of these physiological variables, their interrelationships, and their response to external ameliorations[5], including night working. For example, arterial pressure and body temperature exhibit circadian rhythms. Both are regulated variables that represent the stability and resilience of the body's internal environment and are measurable as physiological responses in a 24-hour window. Both temperature and heart rate are implicated in metabolic homeostasis, yet these factors appear to orchestrate diurnally, independent of each other. Individuals usually fall asleep when the core body temperature decreases and wake when the core body temperature rises.

A biological disturbance in sleep behaviour due to organismal or societal factors is incongruous with daily rhythm in temperature[6]. Phase alterations in closely related cardio-physiological variables due to sleep disruption exhibit dissociative properties due to non-coherence among the underlying phenomena[7]. Systolic (SBP) and diastolic (DBP) blood pressure represent maxima/minima of pressure within the CV system when the heart pumps blood into the arteries and rests to fill with blood before the next contraction. Along with SBP, pulse rate and double product are also predictors of cardiac health[8].

Quantification of peak (acrophase), amplitude and night dip with a focus on waveform alteration of CV rhythms and surface body temperature along with sleep availability would help in understanding inter-shift and inter-individual differences in entrainment to various shift work regimes and the development of chrono-therapeutics for long-term health benefits to shift workers.

Methods

Volunteers

The study protocol was approved by the Human Ethics Committee (HEC, file number CCS-2019/HEC-101 dated 11.2.2019) of Chaudhary Charan Singh University, Meerut, India, in accordance with Indian Council of Medical Research (ICMR) guidelines, India. Initially, 44 healthcare professionals (9 nurses, 9

receptionists, 22 nursing assistants and 4 ward guards) working either in intensive care units, internal medicine wards or outpatient departments consented from a Multi-Speciality Hospital in Meerut India with 300 beds. The inclusion criteria were (1) employed in said hospital, (2) aged 23–40 years, (3) had a body mass index < 25 kg/m^2 and (4) worked in one of the three different shifts: D, N or RS. Work hours of different shifts were regular day shifts (D, from 08.00 h to 18.00 h), rotational days (RD, 08.00 h to 20.00 h) or regular night shifts/rotational nights (RN, from 20.00 h to 08.00 h). Volunteers were not included in the study if they (1) were undergoing any weight-loss program, (2) had suffered sickness or disease in the past 6 months, (3) self-reported thyroid dysfunction, diabetes mellitus, hypertension, etc. (4) had a history of CV diseases (stroke, coronary arterial disease and headed myocardial infarction), (5) were pregnant, (6) had a smoking habit, (7) used sleep drugs, etc. Few volunteers (n = 14) did not join the study for reasons such as smoking habits and discomfort wearing an ABPM. Written informed consent was obtained from 30 volunteers. Data of 2 incompliant volunteers was excluded. Volunteers (n = 28) included 9 D and 9 N, who had unchanged (consistent) routines and 10 RS with fortnightly shift transitions, although 2 RS could not contribute data.

Shift details and observational precautions

Overall, 9 D, 9 N, 7 RD and 10 RN were included for analysis. On Day 1, observations of BMI (body mass index) were taken. Sleep, temperature, food charts and Horne-Ostberg morningness-eveningness (M-E) questionnaires[7] were given. M-E questionnaires are standard scoring procedures of precalibrated questions on diurnal preferences which were not the primary questions investigated; therefore, reliability testing was not needed.

Sleep, CV and temperature rhythm recording

Volunteers recorded BP using a non-invasive, automated oscillometer ambulatory blood pressure monitoring device (ABPM, TM-2430 AnD, Japan) for three days starting at 18:00 h of Day 1. The manufacturer's guidelines and precautions for ABPM were followed. Body temperature was measured manually using a digital thermoscan (ThermoScan, Quick Shot Infrared Thermometer, Exp-01B, Explore, India). For analysis purposes, CT0 (circadian time) was taken as the wake-up time. Sleep/work hour naps were self-reported. Sleep between two shifts was treated as subjective night sleep, while any other sleep episode during work hours was treated as a nap. Repeated measurements of BP of a single individual exhibiting 'within' person variations were treated as random effects. Work-hour nap and night sleep were considered confounding factors for BP variations; thus, there was a fixed effect within a group. No data recorded during off-duty days were included in the analysis.

Data analysis

Circadian parameters, i.e., mesor (circadian mean), amplitude (distance between the maximum and mesor) and acrophase (BP/temperature), were calculated using Cosinor regression analysis. The Wilk-Lambda statistic was calculated by conducting a general linear model using SPSS (IBM. Released 2006. IBM SPSS Statistics for Windows,

V.14.0). D were treated as controls. Nocturnal dipping in BP reflects cardiac health, and that in temperature relates to sleep quality. A 10–20% dip was observed in BP in N and RS, but it either occurred during work hour naps or subjective night sleep between two shifts. Therefore, we categorized volunteers as nap dippers (Napdip) or night dippers (Nitdip). The correlation between BP dip and quality of sleep was also calculated. Acrophase and dip were calculated as maxima and minima by fitting the cosine curve. The phase advance/delay of the test group was estimated as the adjusted geometric mean difference of acrophase predicted for each volunteer in that group and then compared to the respective control. Paired t-tests were used to compare data from the same individuals, while unpaired t-tests were used to compare data from different individuals. Data were analysed using GraphPad Prism ver. 8.0 (GraphPad Software Inc., San Diego, CA, USA). P values < 0.05 were considered significant.

Results

D, N, RD and RN differed significantly in their sleep lengths ($F_{3, 33}$=31.63; P < 0.0001, one-way ANOVA followed by post hoc Tukey's multiple comparisons test), but D and RD (P = 0.925) or N and RN (P = 0.434) did not. Significant differences marked sleep lengths of RD from RN (t_6 = 7.224, P < 0.0005). One-way ANOVA did not reveal significant differences between age ($F_{3, 30}$=0.475, P = 0.702), body mass index ($F_{3, 30}$=1.81; P = 0.333), work experience ($F_{3, 30}$=0.41; P = 0.746) and pulse rate just after waking up ($F_{3, 30}$=1.16; P = 0.341) volunteers working in different shifts. Volunteers had either morning or intermittent chronotype.

Figure 1A, C shows CV rhythm in D. Higher BP at CT12–13 (SBP-141.5±6.9 mmHg; DBP-99.08±8.4 mmHg) was followed by a night dip at CT18 (SBP-98.2±3.2 mmHg; DBP-58.3±2.3 mmHg), i.e., within 3 hours of sleep onset in day workers. A similar bimodal pattern was missing in N, who exhibited acrophase in SBP (CT4; 152.5±6.3 mmHg) and DBP (CT17; 95.3±8.7 mmHg) at different times, but the dip in BP occurred during nap (Fig. 2A and B) at CT11–12 (SBP-111.5±6.4 mmHg; DBP-66.8±5.2 mmHg). Student's t-test revealed a significant difference between SBP (t_{46} = 1.782, P < 0.05) of D and N but not in DBP (t_{46} = 1.06, P = 0.15). Figure 1B, D shows CV rhythm in RS. No conspicuous peak could be observed in SBP (Fig. 2B) and DBP (Fig. 2D) of RS during RD and RN. A night dip at CT18 in SBP among RD (97.3±7.9 mmHg) and at CT23 in RN (113.1±6.2 mmHg) was observed, while there was a night dip at CT19 in DBP among RD (59.5±6.5 mmHg) and at CT23 in RN (67.7±6.1 mmHg). Student's t-test revealed a significant difference between DBP (t_{46} = 1.78, P < 0.05) of RD and RN but not in SBP (t_{46} = 1.53, P = 0.06). However, hours from wake up, i.e., time of physiological day, significantly contributed to BP variations among both D vs. N (SBP- $F_{23, 414}$= 4.117, P < 0.0001; DBP- $F_{23, 414}$=2.516, P < 0.001) and RD vs. RN (SBP only $F_{23, 345}$= 2.56, P < 0.001), as revealed by two-way ANOVA. Body temperature dipping of 1.5°C occurred in D prior to night sleep, whereas N exhibited greater dipping, i.e., up to 2.4°C, that conformed to naps during work hours. Temperatures dipping in RS did not conform to sleep, wake, or nap times; there was an interchange between nap-dipper and night-dipper status during rotating shifts in some volunteers. There were significant differences ($F_{3, 92}$=49.43; P < 0.0001, one-way ANOVA followed by Tukey's multiple comparison test) among the four groups. RS (RD and RN) experienced a significant (t_{23}

= 8.698, P < 0.0001) change in body temperature during the shift transition. The mean temperature of RD and RN was higher than that of the corresponding control groups, i.e., D and N (RD-D = 0.89±0.04; RN-N = 1.2±0.23).

Figure 2 shows that acrophase of systolic and diastolic BP (geometric mean ±SE) occurred in D controls on CT8 and CT7 and in N on CT and CT10.25, respectively. RS exhibited systolic and diastolic BP acrophase at CT7 and CT7.25 hrs during the dayshift that changed to CT9.75 and CT8.6, respectively, during the night shift.

Night and rotational shift work dampened the amplitude of daily rhythm of blood pressure compared to controls. Temperature acrophase (Fig. 2C) occurred at CT-7.48 in D but much later in N (CT-13.45). RS had a higher body temperature that peaked at CT10.4 in RD and CT9 in RN. While a temperature dip in D existed in the initial hour of sleep onset (CT17.2), it was preponed in shift workers (N- CT10.75, RD- CT9, RN- CT14.2). The dynamic changes in additional CV parameters measured by ABPM, i.e., pulse, MAP and double product of BP, exhibited similar daily trends as SBP and DBP in the D ($F_{96, 1249}$=1.203; P = 0.09), N ($F_{96, 1000}$=0.7044; P = 0.98), RD ($F_{96, 750}$=0.81; P = 0.89) and RN ($F_{96, 1125}$=0.78; P = 0.94) groups.

All volunteers exhibited at least a 10% dip in temperature during the day, although few of them exhibited a 20% dip. All D exhibited a night dip (Nitdip) before sleep, which was used as a reference state for comparison in shift workers. Some N and RS also exhibited dipping during naps in work hours (Napdip). A total of 62.5% of N and 44.4% of RN exhibited Napdip, and 50% of RS changed between the Nitdip/Napdip statuses between the day and night shifts (Fig. 3). Daily dip in temperature positively correlated with self-reported quality of night sleep in RS but not in D and N.

A one-way MANOVA revealed statistically significant differences among the changes in systolic, diastolic and temperature rhythms (all shift-work: Wilks' Lambda = 0.094, $F_{(5, 50)}$ = 15.48, $p \leq 0.0001$; N: Wilks' Lambda = 0.055, $F_{(5, 40)}$ = 3.26. $p \leq 0.0001$; RD: Wilks' Lambda = 0.5, $F_{(5, 30)}$ = 3.9. $p \leq 0.0001$ and RN: Wilk's Lambda = 0.30, $F_{(5, 45)}$ = 6.9, $p \leq 0.0001$) with day workers.

Discussion

N recompense their sleep deficit by splitting their sleep/wake schedule (or bifurcating entrainment pattern) to adjust to the challenges of working odd hours.

Sleep differences and napping

Sleep duration varied significantly between day/night shifts (D vs. N or RN, RD vs. N or RN) but not among D-RD and N-RN. That is, half of N and two-thirds of RN took a 1–4 h work-hour nap, showing that night work compulsively displaces sleep to the daytime. Such prophylactic napping helps cope with working odd hours through pacemaker shifting, although the quality of daytime sleep is poorer than that of nighttime sleep[8].

CV rhythm differences

SBP and DBP acrophase/dip (Fig. 1A, C) occurred during the evening/within 3 h of sleep onset in day workers, D, suggesting that synchronous neural autonomic mechanism[9] regulated the daily rhythm of CV functions. Night working, however, differentially affected SBP and DBP; SBP was significantly higher in N than in D, whereas DBP was significantly higher in RN[10] than in RD. Other CV parameters including pulse rate and double product, which are predictors of CV morbidity, also exhibited a robust circadian rhythm in D but not in N or RS.

Blood pressure dipping is a measure of vascular stress recovery. Dampening of BP amplitude in night-shift nurses is indicative of extreme CV stress[11]. Herein, the amplitude of daily rhythm was dampened in N, RD and RN. Additionally, in N and RN, time of dip corresponded either with worktime nap or sleep, returning two BP rise/dip events in a day (Fig. 1A-D). Night shift workers also exhibited reverse dipping, i.e., higher sleep-time BP compared with worktime BP values (Fig. 2B, D, F and H). A direct prognostic implication of the relative importance of dipping pattern[12] and reverse dipping[13] has been reported as a risk factor for cardiac mortality[14]. Scheer and colleagues[15] simulated night work under highly controlled laboratory conditions to understand short-term circadian misalignment due to shift work and reported that this dysregulation increases 24-h blood pressure and inflammatory markers in healthy adults. Blood pressure fluctuations are important predictors of long-term CV health.

Shift work changes circadian properties of temperature

Rotational shift work appeared to dampen the amplitude of the body temperature rhythm, more than D and N. D and N had amplitudes of 0.56^{o}C and 0.67^{o}C, suggesting that N could appropriately adapt by shifting the circadian phase due to persistent routines[16]. Jang[17] observed that temperature amplitude declined in the mid-night-shift routine in RS, being lowest on the remaining days and rising further during the subsequent morning-shift days. We also found the lowest amplitude (0.39^{o}C) in RN group. Frequent alternation of shifts in RS disrupted CR being established during the night-shift period.

Nap duration and time of temperature dipping in shift workers

A thermoregulated dip gates sleep preparation[18] in D, or individuals with consolidated sleep. In N and RN, however, the temperature dip co-occurred with nap during work hours. Temperature and SBP dipping during the work-hour nap suggested synchronized temperature and CV rhythms, thus increasing tolerance for night shift work[19]. Fragmented sleep, although less restorative than consolidated sleep[20], helped N achieve short-term sleep satisfaction[21]. A positive correlation was found (Fig. 3C) between self-reported sleep quality and nap in N. The nap, but not its duration (Fig. 3C), improved sleep satisfaction[22].

Some limitations of the current study included a small cohort size and manually recording body temperature. Study follow-ups were difficult due to frequent job exit of RS compared to D. There are other

important factors, such as food[23–25] and homeostatic drive determined by wakefulness duration[26, 27], which affect body temperature rhythm and sleep.

Sleep bifurcation renders short-term recovery benefits to shift work-driven sleep loss, but its predisposition to long-term CV risk factors implicate circadian pacemaker misalignment. Avenues that might restore circadian alignment in addition to sleep bifurcation in shift workers should be explored. The ability of feeding/fasting cycles to append the sleep/wake cycle in the regulation of physiological and metabolic rhythms[28,29] raises the possibility that intermittent fasting[29] alongside sleep bifurcation may help restore circadian misalignment; this hypothesis needs to be tested in future studies.

Declarations

Conflicts of interest: The authors declare no conflicts of interest.

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Figures

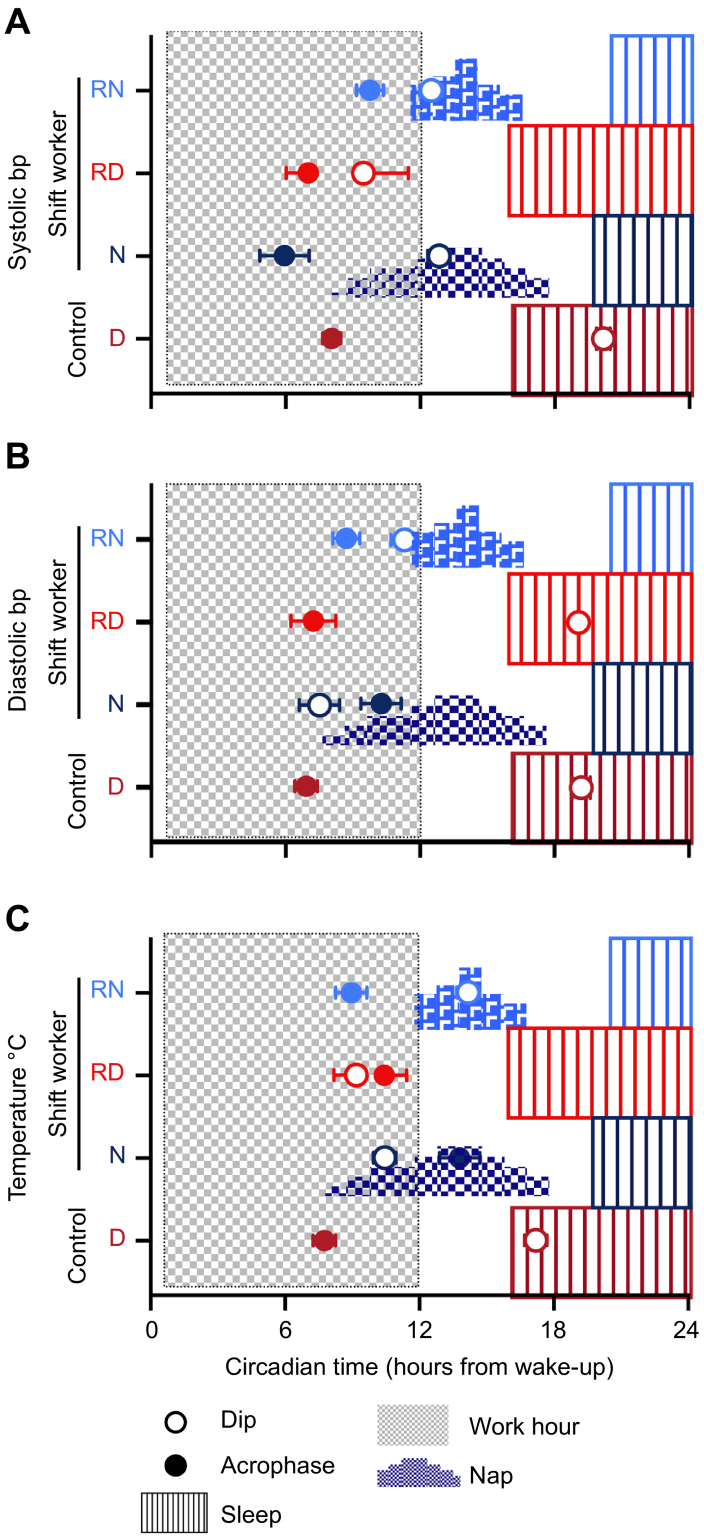

Figure 1

Daily changes (Mean ± SEM) in systolic (A.), diastolic (C.), blood pressure and temperature ^{o}C (E.) in regular Day (D, deep red, solid lines) and night (N, deep blue, broken lines) workers. Daily changes in systolic (B.), diastolic (D.), blood pressure and temperature ^{o}C (F.), in rotational shift workers during day (red, broken lines) and night (blue, broken lines) shifts. The shaded grey area shows working hours, and horizontal-coloured bars show sleep timings.

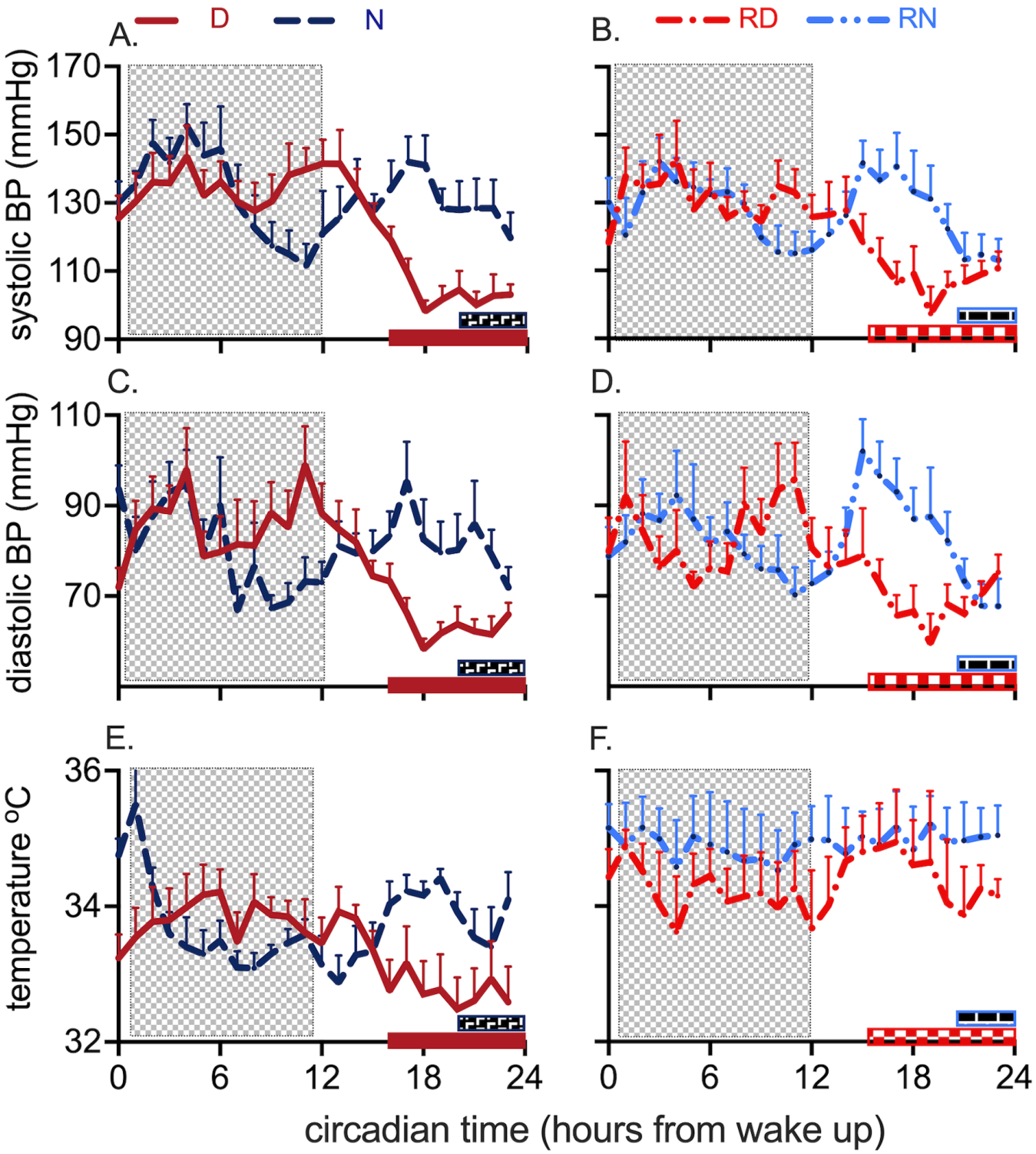

Figure 2

Daily timings (geometric mean ± SEM) of acrophase (closed circles) and dip (open circles) in systolic blood pressure (A.), diastolic blood pressure (B.) and surface body temperature (C.), regular Day (D, deep red) and night (N, deep blue) workers and rotational shift workers during the day (RD, red) and night shift (RN, blue). Shaded grey area shows working hours, coloured pattern without border shows percentage of volunteers taking nap and horizontal-coloured bars with vertical lines show sleep timings.

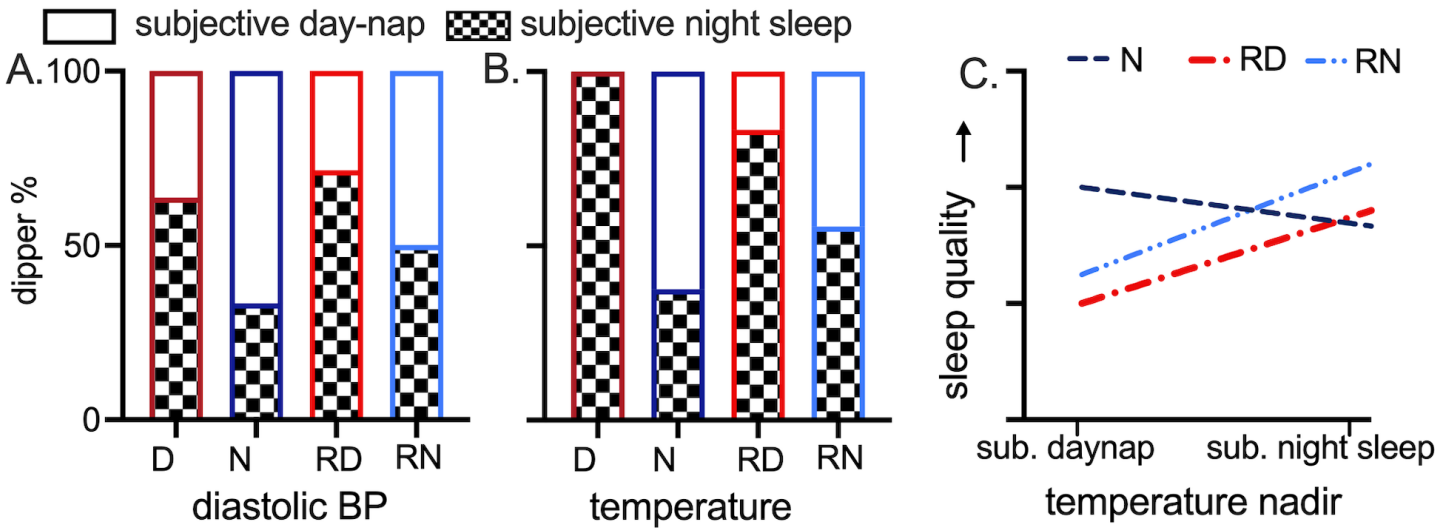

Figure 3

Day workers exhibited daily dip in diastolic BP (A.) and temperature (B.) during the night, whereas shift workers exhibited a dip during work-hour naps. Tendency towards night dipping in temperature was positively correlated in day and rotational shift workers but not in night workers.