

SHORT REPORT

Sleep, Circadian Rhythm, and Cardiovascular Health

Chronological distribution of readings in ambulatory blood-pressure monitoring exams affects the nighttime average and the magnitude of blood-pressure dipping

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Abstract

Averaged nighttime blood pressure (BP) is superior to daytime BP for cardiovascular risk stratification, and the relative change between daytime/nighttime BP (dipping percentage) significantly predicts cardiovascular risk. Newer reports suggest that four measurements at night may be enough for cardiovascular risk stratification. Since BP oscillates across the night, the temporal distribution of measurements across the night may impact nighttime BP and dipping percentage. Therefore, we compared average nighttime BP and dipping percentage when using measurements in the first half (1st half), second half (2nd half), and a combination of both (combined). Forty-three (17 females and 26 males) midlife adults aged 50 ± 10 yr old wore an ambulatory BP monitor for 24 h at home, programmed to measure BP every 20 min when scheduled for daytime and every 30 min during a self-selected 8-h nighttime for time in bed. We compared the nighttime BP averages and dipping percentages when using either the first four measurements from the first half or second half of the nighttime and combined. Nighttime systolic BP was significantly different across first half, second half, and combined (111 ± 9 vs. 107 ± 11 vs. 109 ± 9 mmHg, $P < 0.01$), respectively, with significant pairwise differences across all categories ($P < 0.01$ for each). Systolic BP dipping percentage was significantly different across first half, second half, and combined (9.9 ± 5.5 vs. 13.5 ± 6.4 vs. $11.7 \pm 5.0\%$, $P < 0.01$), respectively, with significant pairwise differences across all categories ($P < 0.01$ for each). Diastolic BP and diastolic dipping percentage were similar across the three different bins. In midlife adults, systolic nighttime BP and dipping percentage may depend upon when BP measurements are taken during the night.

NEW & NOTEWORTHY The distribution of ambulatory blood-pressure monitoring (ABPM) readings affects the reproducibility of average blood pressure (BP) values as well as dipping percentage and dipping diagnoses. Our data suggest that the placement of measurements can affect nighttime average BP. Therefore, the temporal measurement distribution should be considered when interpreting ABPM.

ambulatory blood pressure monitoring; cardiovascular risk; dipping and nondipping blood pressure; hypertension; sleep

INTRODUCTION

Hypertension (HTN) is the leading cause of cardiovascular death and the second leading cause of all-cause mortality in the United States (1). Elevated blood pressure (BP) can cause harm at any time of the day (2), but more than daytime BP, high nighttime BP has been cross-sectionally and longitudinally linked to exacerbated cardiovascular risk and mortality

(3). Furthermore, in comparison with daytime BP, numerous studies have shown greater cardiovascular risk in people whose BP does not decrease by $>10\%$ during the night compared with the daytime (i.e., a 'nondipping' BP profile; 4, 5).

Ambulatory BP monitoring (ABPM) is recommended as the most accurate exam for confirming and treating HTN (6–8). ABPM superiority is partially due to access to BP during



sleep, which is impossible with office BP measures (9, 10). Currently, only the European Society of HTN recommends a minimum of seven readings for successfully interpreting average nighttime BP (7). However, whether this recommendation is based on convenience or a scientific premise is unclear.

Notwithstanding the clinical value of ABPM, these measurements may disturb sleep in some patients, and the number of measurements during the sleep period has been indicated as the main reason behind the discomfort of wearing the ABPM during nighttime (11). With a focus on potentially minimizing the burden for patients wearing ABPM while ensuring correct risk stratification, a recent study by Yang et al. (12) proposed that the minimum number of nighttime ABPM measurements may be reduced to ≥ 4 for cardiovascular risk stratification. This proposed threshold, pending validation, has since been used in numerous large studies of ambulatory BP monitoring to predict risk. In fact, studies have calculated nighttime BP and dipping status using a minimum of three nighttime readings (13, 14). It may be premature to use the minimum threshold of three or four nighttime measurements for risk stratification until the stability of BP across the night using ABPM is established.

BP pattern during sleep is dynamic such that BP decreases after sleep onset, achieving its lowest values at the beginning of the second half of sleep, followed by a slight increase until wake time (15, 16). Therefore, the average BP measured at the beginning of a sleep episode could be different than the average BP calculated during the end of sleep, thus affecting risk stratification. Based on the U-shaped pattern of BP during sleep, we hypothesized that the average BP measured during the first half of the night would be significantly higher than that measured during the second half (15, 16). Consequently, we expected BP dipping to be lower when measurements are taken during the first half of the night compared with the second half.

METHODS

Data included in this analysis were collected from separate studies conducted between 2015 and 2021 that aimed to study sleep and/or circadian rhythms in humans, some of which have been published (17–19). We included participants if their data consisted of at least 20 daytime and 8 nighttime measurements. If participants participated in multiple visits or studies, only their first complete data set was included. We started with 121 files, eliminated 50 duplicates (multiple visits or studies), and excluded another 28 for lack of complete data. We selected the 43 participants for the analyses.

The Institutional Review Board at the Oregon Health and Science University approved the studies for human subject protection. All participants gave a signed written informed consent before enrollment. All methods concerning collecting ABPM data and sleep diaries were identical as part of the screening process for these studies and have been previously published (17–19). Briefly, participants were included when they reported no previous diagnosis of chronic diseases verified by self-report of physical and psychological history. Then, the following preliminary exams were performed to confirm participants' eligibility: resting BP was measured

three times after 5 min of seated rest (Phillips SureSigns VS2⁺ vital signs monitor), body weight and height were measured, and body mass index was calculated. Resting electrocardiogram, at-home sleep apnea screening (WatchPAT; Itamar Medical, Israel), and laboratory testing of hematologic and metabolic measures were reviewed by a physician. We excluded people on any prescription medications, severe obstructive sleep apnea (apnea/hypopnea index ≥ 30 events/h), smoking history (recent use of nicotine confirmed by the presence of cotinine in the urine; NicAlert; Nymox), or use of recreational and opiated drugs verified by urinalysis (Drugsmart 12 panel cup; Speares Medical), or if they were pregnant.

We trained participants to wear an ABPM (Spacelabs Healthcare, Snoqualmie, WA) on nondominant arms for at least 24 h. They were instructed to avoid caffeinated and alcoholic beverages and vigorous physical activity 24 h before and until the end of each ABPM measurement as recommended in the current guidelines for ABPM exams (2). Participants were explained and demonstrated the procedures to don and doff the cuffs in a face-to-face meeting and provided written instructions, such as keeping the arm stable during each measurement. During the measurements, we asked participants to maintain a self-selected 8-h in-bed schedule beginning at their habitual sleep time, for example, 11:00 PM to 7:00 AM, and avoid daytime naps. Sleep and wake times were confirmed by self-report using a sleep diary. BP was programmed to be measured every 20 min during the 16-h day and every 30 min during the 8-h night in each participant. Systolic and diastolic BP average values were calculated for daytime and nighttime. Systolic and diastolic BP dipping percentages were calculated as the percent change between average BP during daytime and nighttime.

Data Analysis

We compared the calculated average of systolic and diastolic BP and dipping percentage between the first half of the night (i.e., the 1st 4 h of time-in-bed schedules as indicated by the sleep diary, 1st half), the second half (i.e., the last 4 h, 2nd half), and the combined average. Using four as the minimum number of measurements during nighttime, as Yang et al. (12) suggested, the first four measurements from each half and a combination of both were used to calculate the "bins." Furthermore, comparing the first four measurements in each half allowed for the inclusion of the greatest number of measurements per participant in each half without incurring measurement bias. Repeated-measures ANOVAs were used to compare average BP and dipping percentage, respectively, between first half, second half, and combined sleep. An alpha level of 0.05 was used for all analyses to infer statistical significance. Post hoc analysis was employed using Bonferroni corrected *t* tests when the *P* value of the ANOVA test was <0.05 . *P* values are reported exactly except when lower than 0.01. All analyses were conducted using RStudio software (RStudio Team, 2020) and SAS 9.4.

Exploratory Analyses

We did additional exploratory testing to examine whether different data binning than our a priori hypothesis resulted

in differences in BP across the night. Specifically, we took three BP measures across the night (at *hours* 2, 4, and 6, akin to 1st half and 2nd half of the night) and used *t* tests comparing *hour* 2 versus the bin of *hours* 4 and 6, and each of those against a combined average of all (i.e., *hours* 2, 4, and 6).

RESULTS

Forty-three participants were included in the analysis. The physical and clinical characteristics of the participants are described in Table 1, which includes 11 participants identified with untreated mild hypertension and 6 with untreated moderate sleep apnea during screening.

Comparisons among First versus Second Half and Combined BP

Nighttime average systolic BP was significantly different across first half, second half, and combined (111 ± 9 vs. 107 ± 11 vs. 109 ± 9 mmHg, $P < 0.01$; Fig. 1A), with significant pairwise differences among the three categories ($P < 0.01$ for each). Nighttime diastolic BP was similar among the three different bins of readings (63 ± 6 vs. 62 ± 7 vs. 62 ± 7 mmHg, $P = 0.17$; Fig. 1B), respectively.

Systolic BP dipping percentage was significantly different across first half, second half, and combined (9.9 ± 5.5 vs. 13.5 ± 6.4 vs. $11.7 \pm 5.0\%$, $P < 0.01$; Fig. 1C), with significant pairwise differences among the three categories ($P < 0.01$ for each). Diastolic BP dipping percentage was similar among the three different bins of readings (16.5 ± 7.6 vs. 18.5 ± 8.3 vs. $17.5 \pm 6.6\%$, $P = 0.15$; Fig. 1D), respectively.

Exploratory Analyses

We observed that the measurement at *hour* 2 was significantly higher than the combination of *hours* 4 and 6 (111 ± 9 vs. 104 ± 10 mmHg, $P < 0.001$) and the combination of the average of *hours* 2, 4, and 6 (111 ± 9 vs. 107 ± 8 mmHg, $P < 0.001$). The combination of *hours* 4 and 6 was lower than *hours* 2, 4, and 6 (104 ± 10 vs. 107 ± 8 mmHg, $P < 0.001$). Furthermore, we compared this new full combination (i.e., *hours* 2, 4, and 6) versus the combined data (1st half + 2nd half) presented in the current study. In this comparison, we found that the combined data's average was higher than *hours* 2, 4, and 6 (109 ± 9 vs. 107 ± 8 mmHg, $P = 0.013$).

Table 1. Baseline characteristics of participants

Characteristic	
Total participants, <i>n</i>	43
Sex (female), <i>n</i> (%)	17 (39.5)
Age, yr	50 ± 10
Height, cm	176.2 ± 11.0
Body mass, kg	83.8 ± 16.1
Body mass index, kg/m ²	27.0 ± 4.5
Systolic blood pressure, mmHg	121 ± 13
Diastolic blood pressure, mmHg	69 ± 9
Blood glucose, mg/dL	93 ± 10
Apnea-hypopnea index, events/h	9.2 ± 7.4
Average time to bed, h:min	$22:46 \pm 1:06$
Average wake time, h:min	$06:48 \pm 1:07$

Values are means \pm SD or number of participants, *n* (%). Blood pressures were measured in triplicate in the office during screening visits. h:min, hour:minute as reported by participants.

DISCUSSION

In this secondary analysis, we investigated if the distribution of ABPM readings across the night could affect the average BP and BP dipping status, comparing data across the two halves of an 8-h nighttime. We found that the chronological distribution of BP readings during the nighttime affects systolic BP average and dipping percentage and could thus affect risk stratification.

The BP pattern during sleep may somewhat explain the differences found in the current study. First, there is a clear U-shape pattern in BP during sleep, with the lowest values usually achieved at the beginning of the second half of sleep, followed by a slight increase until wake time (15, 16). The absolute values right after the sleep starts are still higher than the last values before the wake time (15). Second, the sleep architecture comprises two different sleep patterns: N-REM and rapid eye movement (REM) sleep. During REM sleep, changes in BP control occur because of an increase in sympathetic outflow promoting vasoconstriction (20). N-REM sleep is characterized by predominantly slow and high-voltage waves that dictate low brain activity with limited movement detected in the eyes. In this phase, BP remains low, which occurs in parallel with regular breathing and heart rate (21). Thus, BP measures at the beginning of the first half of nighttime (i.e., BP transitioning between awake and sleep) in comparison with those obtained at the second half of nighttime (i.e., usually lowest BP values during sleep) may directly impact average BP during sleep and subsequently dipping status similarly to as found in the current analysis.

We found differences of the magnitude of ~ 4 mmHg between first half and second half of the night. These differences were also reflected in a lower systolic BP dipping percentage in the first half of -3.3% and -1.7% , compared with the second half and combined. In fact, on average, first-half measurements would classify participants as nondippers compared with dippers in the second half and combined. A previous study compared different approaches to determine nighttime, such as diary, actigraphy, and fixed times. Similar to our findings, they also found similar differences in BP magnitude, albeit to a smaller degree (~ 2 mmHg) when using different approaches (22). In our study, BP measurements collected during first half of the night could be higher either because they are affected by wakefulness before sleep, because of the expected pattern during sleep, or both (15, 16).

Our data add the placement of measurements as a potential factor to be considered when attributing risk from ABPM data. Indeed, it has been shown that a narrow-fixed time method (i.e., between 1:00 AM and 6:00 AM) is more reproducible than a wide-fixed method (i.e., 11:00 PM to 7:00 AM) to determine nighttime BP and dipping status (23). Given that ABPMs can be programmed to start data collection at certain times, collecting data in a narrow window during the night may be considered in future studies. Our results add to the vastly developing literature showing low reproducibility of dipping patterns (24). All studies, especially intervention studies in this area, must perhaps test the stability of nighttime measurements and the reproducibility of their results using different approaches to calculate nighttime BP and the magnitude of dipping.

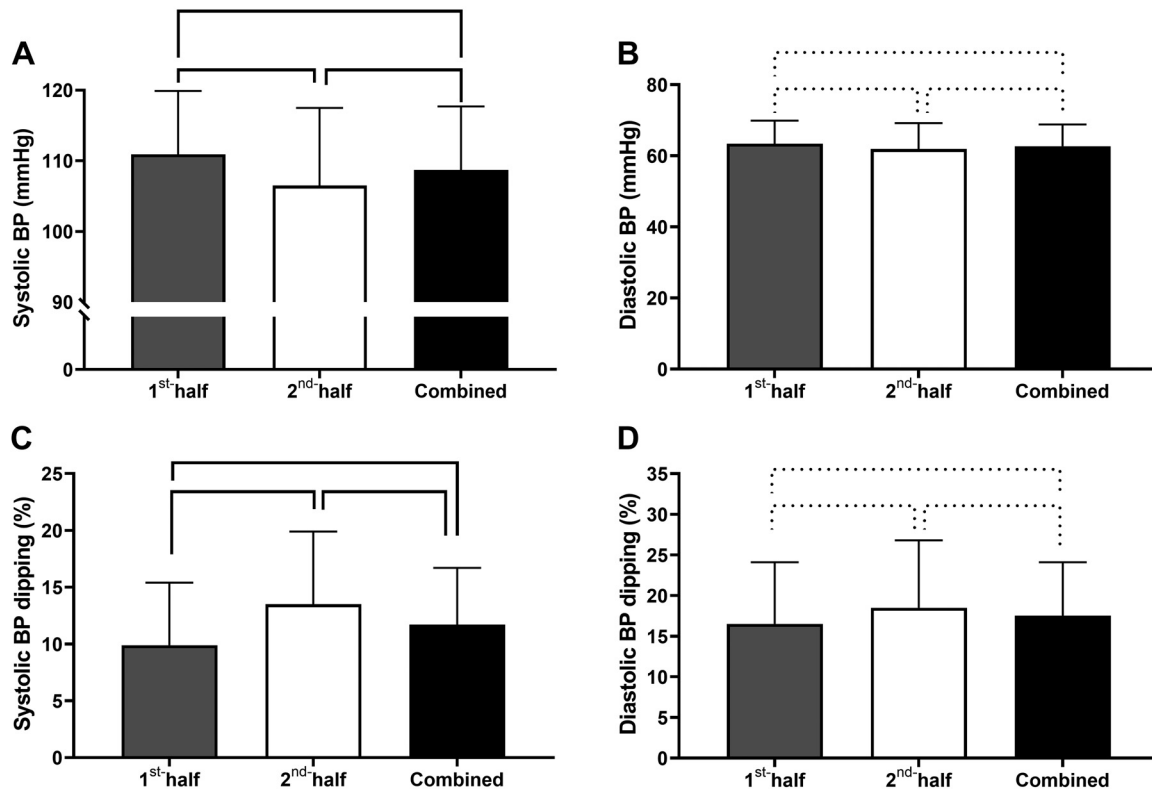


Figure 1. Comparison of the average nighttime systolic and diastolic blood pressure (A and B) and systolic and diastolic blood-pressure dipping percentage (C and D) calculated using the first four measurements of the first half of the night (1st half), 1st four measurements of the second half of the night (2nd half), and both sets of data combined. Solid lines indicate pairwise differences ($P < 0.05$), and dashed lines indicate no difference ($P > 0.05$). We used Bonferroni-corrected tests. Data are presented in means \pm SD.

The current study presents several strengths, including ecological validity, but also has limitations. The main strength was that bedtime and wake time were self-selected and verified accurately using each participant's sleep diary rather than an arbitrary "nighttime." This methodology aligns with previous ABPM studies reporting consistency in bedtime and wake times obtained from diaries and actigraphy (25). In addition, a recent study identified the ABPM averages were more reproducible using participants' diaries than the actigraph (22). Due to the self-selected 8 h in bed, the nighttime period was 8 h for each participant. One limitation is a lack of polysomnography simultaneously with ABPM. The absence of an objective measure of sleep does not allow us to guarantee that any difference was due to the presence or absence of sleep or different sleep stages. However, risk stratification has been consistently attributed to a fixed time or self-reported sleep time to calculate nighttime averages of BP values (3–5, 24, 26), which is closer to the strategy performed in this study. Second, the results should not be generalized to elderly individuals since the sample comprises young and midlife adults. Third, we included people with common disorders such as untreated hypertension and moderate sleep apnea but excluded more severe conditions (e.g., severe sleep apnea) to limit the variability in ABPM values (27–29). Fourth, the choice of four measurements is based on the minimum threshold suggested by Yang et al. (12), the results are protocol dependent and could be different if increasing or decreasing the number of measures or changing the duration of sleep opportunity. Fifth, the placement of measurements used for analysis (1st half vs.

2nd half) was done to avoid data overlap and is only one scenario, but it supports the thought that four nighttime measurements are not an accurate representation of the average nighttime BP or dipping status. It is also important to note that the average differences between the halves of the night (~ 4 mmHg) are significant but less than the standard deviations (≥ 9 mmHg) of these category measures. Furthermore, our exploratory analyses suggest that independent of the demarcation of time, BP measures taken at different times of the night could lead to different interpretations. Thus, the indirect BP measures on single measures in individuals compared with repeated measures and collective group measure differences may be susceptible to misinterpretation bias.

In conclusion, in midlife adults, systolic nighttime BP and dipping percentage may depend upon when BP measurements are taken. The minimum threshold of four is affected by measurement placement and may interfere with a precise diagnosis and risk attribution. More rigorous prospective studies in this area will help reconcile the dilemma between the clinical utility and physiological accuracy and precision of ABPM.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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DISCLOSURES

A.W.M. reports consulting for Pure Somni, Inc; nothing related to this work. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

L.C.B. and S.S.T. conceived and designed research; N.P.B., A.W.M., M.P.B., J.S.E., S.A.S., and S.S.T. performed experiments; L.C.B., S.S.T., and S.P.M.R. analyzed data; L.C.B., N.P.B., A.W.M., S.P.M.R., M.P.B., J.S.E., S.A.S., and S.S.T. interpreted results of experiments; L.C.B. prepared figures; L.C.B. and S.S.T. drafted manuscript; L.C.B., N.P.B., A.W.M., S.P.M.R., M.P.B., J.S.E., S.A.S., and S.S.T. edited and revised manuscript; L.C.B., N.P.B., A.W.M., S.P.M.R., M.P.B., J.S.E., S.A.S., and S.S.T. approved final version of manuscript.

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