Published in final edited form as:

Blood Press Monit. 2020 April ; 25(2): 61–68. doi:10.1097/MBP.0000000000000426.

Blood Pressure Monitoring in Sleep: Time to Wake up

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Abstract

Hypertension is a highly common condition with well-established adverse consequences. Ambulatory blood pressure (BP) monitoring has repeatedly been shown to better predict cardiovascular outcomes and mortality, compared to single office visit BP. Non-dipping of sleep-time BP is an independent marker for increased cardiovascular risk. We review BP variability and the challenges of BP monitoring during sleep. While pathological sleep such as obstructive sleep apnea has been associated with non-dipping of sleep-time BP, BP is not routinely measured during sleep due to lack of unobtrusive BP monitoring technology. Second, we review existing noninvasive continuous BP monitoring technologies. Lastly, we propose including sleep-time BP monitoring during sleep studies and including sleep studies in patients undergoing ambulatory BP monitoring.

Keywords

ambulatory blood pressure monitoring; blood pressure; hypertension; sleep; sleep apnea

Introduction

Despite the increasing number of scientific reports emphasizing the value of ambulatory blood pressure monitoring (ABPM) for the accurate diagnosis and better risk stratification of hypertension (HTN), the clinical use of ABPM in real-world practice is highly limited. The diurnal nature of blood pressure (BP) is a well-established concept. However, the importance of BP measurement in sleep has rarely been fully appreciated. Knowledge of sleep-time BP would improve risk prediction of patients with HTN and may allow better therapeutic

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strategies (e.g., timing of antihypertensive medications) in some patients. It would also allow personalized treatment of obstructive sleep apnea (OSA), as the effect of OSA on BP varies considerably between patients. In this article, we will discuss the factors altering sleep-time BP, the importance of sleep-time BP measurement, and plausible methodologies for BP measurement during sleep. The topic of sleep and HTN has been extensively reviewed in the past and will not be the focus of this review.(1, 2)

1. Blood pressure Variability

HTN is a well-established cardiovascular risk factor. However, the diagnosis and evaluation of HTN is complicated since BP normally fluctuates, not only because BP follows an intrinsic circadian rhythm, but also because BP is constantly responding to extrinsic stimuli. Appreciation of BP variability raises the issue of how to accurately measure BP in the face of variability that exists from minute to minute to a range that expands over years/decades. BP variability is encountered frequently in clinical practice, with some patients reporting highly fluctuating BP measurements throughout the day and others showing markedly different BP measurements between separate office visits months or years apart. In addition to behavioral, neural, reflex, humoral, and environmental factors, circadian rhythm contributes to this variability.(3, 4) Given the variable nature of BP, ABPM is more advantageous in demonstrating more averaged BP and short term BP variability.(5) Furthermore, ABPM improves the prognostic value of a single office BP measurement when predicting mortality (6-9) and adverse cardiovascular consequences.(10, 11) Superiority of ABPM to clinic BP was recently confirmed in a large Spanish national registry-based cohort.(9) These findings were further reviewed and summarized by Piper et al.(12)

2. Sleep-time Blood Pressure

BP has circadian pattern primarily modulated by sleep-wake state. While BP decreases in the night during sleep, it prominently increases in the morning shortly before awakening. This BP surge corresponds to peak acute cerebrovascular and coronary events in the early morning.(13) Typically a 10-20% sleep-time BP decrease is expected. Lack of such a decrease is abnormal and is called ‘non-dipping’. Another abnormal BP pattern is reversed dipping, which is defined as higher average sleep-time BP than daytime BP. Both non-dipping and reversed dipping have been associated with a higher risk of increased left ventricular mass, increased carotid intima-media wall thickness and plaque burden, silent cerebral infarction, and microalbuminuria.(14) Non-dipping has also been associated with increased cardiovascular mortality in proportion to lack of dipping in both normotensive and hypertensive patients.(15) In a study of an Italian community-based cohort Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) that performed ABPM, non-dipping was the strongest predictor of cardiovascular mortality.(7) Subsequent systematic review also demonstrated that non-dipping was the most consistent predictor of subclinical and clinical cardiovascular morbidity and total mortality in both hypertensive patients and the normotensive population.(16, 17) In contrast, daytime BP, when adjusted for sleep-time BP, was not a significant predictor of overall or cardiovascular mortality in hypertensive patients, but was a significant predictor of cardiovascular morbidity in the normotensive population.(16) Interestingly, ‘isolated sleep-time HTN’ (defined as no evidence of HTN by office BP

or daytime ABPM measurement) independently predicts an increased risk of subclinical and clinical cardiovascular disease.(18, 19) In contrast, pathological sleep, such as OSA, periodic limb movements (PLMs) or frequent arousals may contribute to non-dipping and will be discussed below. While BP decreases overnight during sleep, it prominently increases in the morning shortly before awakening.(13) This morning BP surge (MBPS) has gained significant interest because the timing of the morning BP surge corresponds to peak cardiovascular events such as acute myocardial infarction, stroke, and sudden death.(20) MBPS is also associated with increased arterial stiffness and endothelial dysfunction.(21)

Effect of obstructive sleep apnea on sleep-time blood pressure

OSA is a highly common syndrome that affects at least 10-15% of adults in the general population.(22) OSA is characterized by recurrent episodes of upper airway obstruction that can lead to hypoxemia/hypercapnia and arousal. Somers et al. in their landmark study showed increased sympathetic nerve activity and BP during OSA events. In addition, they showed that awake sympathetic nerve activity is increased in patients with untreated OSA implying that the sympathomimetic effect of OSA may persist into the day.(23) Chronic sympathetic overactivity induced by untreated OSA may contribute to autonomic dysregulation and HTN.(24) In support of this, numerous epidemiologic studies have linked OSA to HTN.(25) In the Wisconsin Sleep Cohort, severity of OSA was associated with incident HTN during a four year follow up.(25) Post-hoc analysis also revealed that severity of OSA observed in rapid eye movement (REM) sleep is associated with incident HTN, independent of overall OSA severity, highlighting sleep stage specific cardiovascular vulnerability.(26) OSA is considered to be an important risk factor for non-dipping BP patterns, sleep-time HTN and surges in morning BP.(27, 28) In addition, OSA has been associated with high sleep-time BP variability as assessed by ABPM.(29, 30) Excessive short-term sleep-time BP variability has been linked to target organ damage and cardiovascular disease.(31) Thus, sleep-time BP during sleep may not only be the link between OSA and cardiovascular disease, but also may confer important prognostic information in patients with OSA. In considering OSA's effect on sleep-time BP, it is critical to understand that OSA in two patients might result in a similar frequency of obstructive respiratory events yielding a similar degree of OSA severity by conventional criteria but may have very different effects on BP.

Effect of periodic limb movement on sleep-time blood pressure

PLM is defined as an uncontrollable rhythmic movement of the extremities that occur during sleep. Studies have shown that PLM leads to rise in BP.(32, 33) In one study the highest BP rise was seen with respiratory related limb movement (systolic blood pressure (SBP) 18.9+/−14.9 mm Hg) followed by PLM with (SBP 16.7+/−9.4 mm Hg) and without arousal (SBP 11.2+/−8.7 mm Hg).(32) This may represent one mediating mechanism of PLM's association with increased risk for cardiovascular disease.(34, 35) PLM is common in patients with restless leg syndrome (RLS) but is not uncommonly detected during routine sleep study in patients without any history of RLS.(36, 37) Thus, the possibility of coexisting PLM should be considered in interpretation of ABPM that shows sleep-time BP elevation.

Effect of arousals on sleep-time blood pressure

Arousal from sleep is considered a marker of sleep disruption and can be associated with increased respiratory efforts, limb movement, or can be spontaneous in nature.(38, 39) Arousals induce autonomic change, resulting in increases in BP and heart rate.(40, 41) Davies et al. showed that in subjects without HTN, average systolic BP rose by 6 (during rapid eye movement (REM) sleep) ~ 10 mmHg (during non-REM) following cortical arousal compared with control values.(40) In that study, stimuli that did not cause electroencephalogram (EEG) arousal still led to BP rise albeit to a lesser degree implying the existence of subcortical “autonomic arousal.” This study also revealed that BP as measured by beat-to-beat BP monitor from the other arm increases with the activation of cuff-based ABPM, suggesting overestimation of BP by current standard ABPM technique. Another study showed that patients with HTN have a more exaggerated BP response to arousal than normotensive patients.(42) Thus, arousal induced increases in BP may represent one mechanism by which poor sleep quality is associated with HTN.(43)

Effect of short sleep duration on sleep-time blood pressure

Since BP typically dips in sleep, reduction in sleep time itself can lead to greater exposure to relatively higher BP over a 24-hour period (i.e., shorter sleep-time dipping period). Moreover, insufficient sleep can lead to increased BP the following day and night.(44) These mechanisms may be partly responsible for the association of short sleep duration and HTN. In the first National Health and Nutrition Examination Survey of middle-aged adults, self-reported short sleep duration was predictive of incident HTN.(45) In the Coronary Artery Risk Development in Young Adults cohort, actigraphy-estimated sleep duration was associated with incident HTN with each hour of reduced sleep being associated with a 37% increase in the odds of incident HTN.(46)

3. Challenges in sleep-time blood pressure measurement

Despite the valuable information acquired from monitoring BP during sleep, BP is not routinely measured, in part because there is no minimally intrusive ABPM technology. Other considerations include non-recognition of the value of ABPM in making accurate diagnosis of BP status, non-payment by health insurance organizations for the procedure, and perceived disruption by clinicians of the clinical routine. Sleep-time BP, if it can be easily measured, would be a powerful physiological measurement to assess and would provide insight into the individual’s sleep-time BP pattern. However, still today there are considerable technical challenges to obtaining this data. One challenge is that “cuff-based” ABPM is the only widely available test to assess sleep-time BP. Frequent inflation and deflation of BP cuff (approximately every 15 minutes during the day to 30 minutes during the night) can easily disturb sleep.(47, 48) In one study with subjects who underwent polysomnography and ABPM, cuff inflation was associated with increased arousal and wakefulness. Subjects in that study recalled about 58% of cuff inflation episodes.(49) Through these sleep interruption, cuff inflation can cause falsely elevated BP.(50) Thus, in patients that perceive poor sleep during ABPM, sleep-time BP may not be accurate and prognostic significance of sleep-time BP is diminished.(51) Emerging cuff-based watch-like wrist devices may be less intrusive and prove to be useful.(52) Another challenge is time

stamping of BP measurements that occur during sleep. Ideally sleep-time BP timing should coincide with sleep period. Unfortunately, at this time, there is no objective way to determine sleep and wake during ABPM collection, other than using a self-reported diary which can bias the analysis and interpretation of sleep-time BP.(53) While sleep diary appears acceptable, objective sleep onset/offset time assessment with a tool such as actigraphy provides more accurate circadian ABPM data.(53, 54) In this regard, it would be of interest to posit if the concurrent use of consumer wearable devices that can measure activity level may add any value to more accurate ABPM assessment.

4. Continuous noninvasive blood pressure monitoring techniques

Current cuff-based ABPM is periodic in nature with BP measured every 15 to 30 minutes. While this may be sufficient to ascertain average BP and diurnal pattern over 24-hour period, more frequent “continuous” BP measurement allows more in-depth analysis of how BP evolves in real-time.

Continuous BP measurement typically requires invasive arterial catheterization. For obvious reasons, such as invasiveness and potential complications, arterial lines are impractical in the ambulatory setting. Recently, technical advances have produced a number of devices available for cuff-less continuous beat-to-beat BP monitoring (Table 1).

Volume-clamp (vascular unloading) technique, or the “Penaz” method has been available for a few decades. This technique is based on the principle that BP can be estimated by measuring finger cuff pressure required to maintain constant volume of blood flowing in the finger.(55) The majority of research involving noninvasive continuous BP monitoring used the device based on this method. Several products are commercially available: Finapres® (Finapres Medical Systems, Enschede, Netherlands), continuous noninvasive arterial pressure (CNAP®) (CNSystems, Graz, Austria) and ClearSight system (Edwards Lifesciences, Irvine, CA, USA). These devices are FDA approved and are mainly used as a noninvasive hemodynamic monitoring in the hospital setting (Figure 1a). Limitations of this technology include lower accuracy in low perfusion state and time lag.(56, 57) In addition, this method is partly intrusive because of discomfort resulting from finger clamping. Despite one study that demonstrated no significant difference in sleep quality between subjects with and subjects without Portapres® (an ambulatory version of Finapres®) in sleep, its use to acquire ABPM has been limited to research settings due to expense and finger discomfort. (58)

Applanation tonometry technology is commonly used to analyze pulse wave contour and has been explored as a method to obtain continuous BP measurements. This technique involves the compression of the radial artery, enough to flatten it but not occlude it, and the pressure required to flatten the artery is used to derive BP using an algorithm (Figure 1b).(59) Recently, a device based on this method was developed (Beat By Beat® by Omron Healthcare, Kyoto, Japan) but is not yet commercially available. Limitations of this technology is that measurements are very sensitive to movement and validation studies are still needed.

Pulse transit time (PTT) is based on the concept that there is an inverse relationship between change in vascular stiffness (which is predominantly influenced by BP) and change in pulse wave velocity.(60) PTT is typically measured from a photoplethysmogram signal and highly correlates with cuff-based and intraarterial BP measurements.(61, 62) Since PTT is based on the time interval between ECG R wave to pulse arrival time which includes the varying degree of pre-ejection period, a limitation of this technology is the need for frequent calibration. Despite this, PTT appears to be useful in tracking change in systolic BP.(63) There are two commercially available devices that are based on this technique, including the FDA approved Sotera ViSi Mobile® continuous noninvasive BP (cNIBP) monitor (Sotera Wireless, Inc. San Diego, CA, USA) and the SOMNOtouch™ NIBP system (SOMNOmedics, Randersacker, Germany) (Figure 1c). SOMNOtouch™ NIBP can be integrated into polysomnography produced by the same company allowing simultaneous recording of BP and polysomnography parameters.

Pulse decomposition analysis extracts various pulse reflection points in deriving parameters needed to calculate systolic BP and pulse pressure. This technology employs a low-pressure finger cuff inflation technique to extract the pulse wave form. Caretaker® (Caretaker Medical, Charlottesville, VA, USA) is an FDA approved device that has been validated against invasively-measured arterial pressure (Figure 1d).(64, 65) Since this device only requires a one-time initial calibration and the low cuff pressure is relatively comfortable and well tolerated, this device has the potential to be used to obtain continuous BP measurements during sleep.

Use of the aforementioned continuous noninvasive BP monitoring methods has been largely limited to the research setting. Although these technologies are still undergoing development and validation clinical studies, alternatives to cuff-based ABPM will likely have a significant impact on more widespread adoption of ABPM in clinical practice.

5. Continuous noninvasive blood pressure monitoring during sleep study

Polysomnography, which is the gold standard sleep study, comprehensively records multiple physiologic parameters including electrogram monitoring of superficial brain waves, ocular movement and muscle tone of chin and limbs, respiration (airflow and effort), oxygen saturation and an electrocardiogram. Home sleep study using a portable sleep monitor is typically equivalent to respiratory polygraphy with the recording limited to respiration parameters (airflow, effort and oxygen saturation). Currently, BP monitoring is not part of the parameters obtained in any form of sleep study (Figure 2). This is not due to lack of perceived need in practice but rather due to absence of nonobtrusive and reliable methods. Among the aforementioned continuous noninvasive BP monitoring techniques, volume-clamping method using Finapres® has been the modality of choice.(23, 30, 66) PTT-based SOMNOtouch™ system is available for clinical use as a stand-alone or as a part of a sleep study module. Moreover, available studies examining the accuracy of the system are limited. (67, 68). Applanation tonometry technology has also been used in the sleep study setting. (69) Currently, there is no custom software synchronizing BP data from the Caretaker system with the sleep study but it is under development.

6. Assessment of sleep during sleep-time ambulatory blood pressure monitoring

Given the aforementioned link between sleep and sleep-time BP, concurrent assessment of sleep during ABPM would be valuable in better understanding the pathophysiology of sleep-time BP at an individual patient level. However, sleep-time BP as measured by conventional cuff-based ABPM should be interpreted with caution since BP surges in response to apnea/hypopnea respiratory events can be missed by intermittent nature of the measurement. This was well-illustrated by Kario et al. who uncovered much higher sleep-time BP measurement when sleep-time BP triggered by peripheral (finger-tip) oxygen desaturation (a desaturation-triggered BP monitoring system) was applied than by standard intermittent ABPM. (70, 71) This challenge can be overcome by minimally intrusive continuous noninvasive BP monitoring. Importantly, since sleep disorders such as OSA can be treated, OSA assessment, preferably conducted simultaneously with ABPM, would help researchers and clinicians personalize management and treatment strategies.

7. Future aspects in adopting continuous blood pressure monitoring in sleep

Technological advances in continuous noninvasive BP measurements that are accurate and simple to use should encourage sleep research and allow incorporation of sleep-time BP monitoring into clinical sleep studies. Currently there is a shift from a single in-lab polysomnography to multi-night portable home sleep studies which would benefit from the inclusion of sleep-time BP measurements. Future advances will be needed in both hardware (development of adaptable BP display) and software (systematic approaches to converting continuous BP data into more easily understood physiologic parameters). Finally, analyses of noninvasive continuous BP measurements during sleep studies would significantly enhance machine learning techniques already employed to understand the heterogeneous OSA population and cardiovascular outcomes.

Acknowledgments

Conflicts of Interest: Younghoon Kwon has given a talk sponsored by Caretaker Medical and received reimbursement for travel. This work was partly supported by NIH R21 HL140432. No others have declared any conflicts of interest.

Abbreviations

ABPM	ambulatory blood pressure monitoring
BP	blood pressure
cNIBP	continuous noninvasive BP
EEG	electroencephalogram
HTN	hypertension
MBPS	morning blood pressure surge

OSA	obstructive sleep apnea
PLMs	periodic limb movements
PTT	pulse transit time
REM	rapid eye movement
RLS	restless legs syndrome
SBP	systolic blood pressure

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Figure 1. Noninvasive continuous blood pressure monitoring devices

a. ClearSight System (Edwards Lifesciences) b. T-Line (Tensys Medical)†
c. Somnotouch (SOMNOmedics) d. CareTaker (Caretaker Medical)
†T-Line is currently not commercially available.

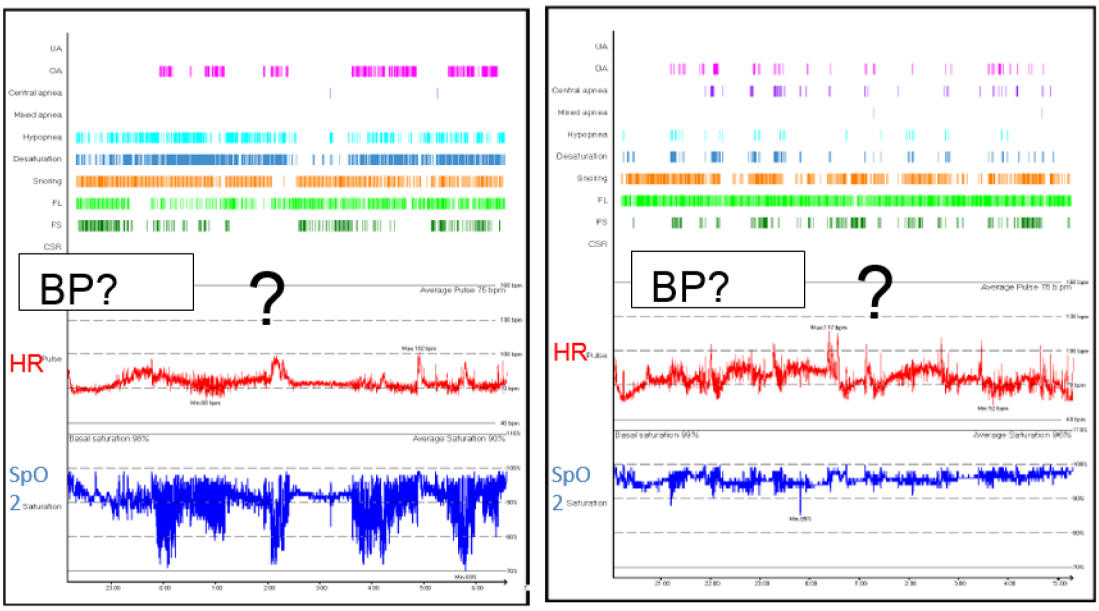

Figure 2. Typical portable sleep monitor recording

Illustration of portable sleep study summary depicting results from two different patients with similar degree of OSA severity by apnea hypopnea index (AHI). Highlighting marked difference in degree of oxygen desaturation between the two patients with similar AHI. SpO2 (in blue): pulse oximeter-derived peripheral oxygen saturation, HR (in red): heart rate. “BP?” (blood pressure) points out that it is not part of the routine sleep study.

Table 1.

Characteristics of Non-Invasive Blood Pressure Monitors

Blood Pressure Technology	Mechanism of Measurement	FDA / CE Approval?	Commercially Available?	Current Use in Clinical Sleep Practice?	Validated?	Validated Against?	Validation Setting
Finapres® (57)	Volume-clamp	Yes / Yes	Yes	No†	Yes	Continuous invasive intra-arterial catheter	In-hospital floor patients
CNAP® (55, 71)	Volume-clamp	Yes / Yes	Yes	No	Yes	Continuous invasive intra-arterial catheter	Surgical patients under general anesthesia
ClearSight (72, 73)	Volume-clamp	Yes / Yes	Yes	No	Yes	Continuous invasive intra-arterial catheter; Mercury sphygmomanometer	Surgical patients under general anesthesia; Outpatient clinic
Beat By Beat® (74)	Applanation tonometry	Yes / Yes	No	No	Yes	Mercury sphygmomanometer	Outpatient clinic
Sotera ViSi Mobile® (75)	Pulse Transit Time	Yes / Yes	No	No	Yes	Mercury sphygmomanometer	In-hospital floor patients
SOMNOtouch™ (76)	Pulse Transit Time	Yes / Yes	Yes	Yes	Yes	Mercury sphygmomanometer	Outpatient clinic
Caretaker® (63, 77)	Pulse decomposition analysis	Yes / Yes	Yes	No	Yes	Continuous invasive intra-arterial catheter	Surgical patients under general anesthesia

†Finapres technology has been used in a sleep research setting.