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Association of novel measures of sleep disturbances with blood pressure: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—Mechanisms underlying blood pressure (BP) changes in obstructive sleep apnoea (OSA) are incompletely understood. We assessed the associations between BP and selected polysomnography (PSG) traits: sleep depth, airflow limitation measurements and OSA-specific hypoxic burden.

Methods—This cross-sectional analysis included 2055 participants from the Multi-Ethnic Study of Atherosclerosis who underwent PSG and BP measurements in 2010–2013. Sleep depth was assessed using the 'OR product', a continuous measure of arousability. Airflow limitation was assessed by duty cycle (T_i/T_t) and % of breaths with flow limitation, and hypoxia by 'hypoxic burden'. Primary outcomes were medication-adjusted systolic BP (SBP) and diastolic BP (DBP). We used generalised linear models adjusted for age, sex, race/ethnicity, smoking, education, body mass index, alcohol use, periodic limb movements and alternative physiological disturbances.

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Results—The sample had a mean age of 68.4 years and apnoea–hypopnoea index of 14.8 events/hour. Sleep depth was not significantly associated with BP. Every 1 SD increment in log-transformed non-rapid eye movement duty cycle was associated with 0.9% decrease in SBP (95% CI: 0.1% to 1.6%), even after adjusting for sleep depth and hypoxic burden. Every 1 SD increment in log-transformed hypoxic burden was associated with a 1.1% increase in SBP (95% CI: 0.1% to 2.1%) and 1.9% increase in DBP (95% CI: 1.0% to 2.8%) among those not using hypertension medications.

Conclusions—Higher duty cycle was associated with lower SBP overall and hypoxic burden with higher SBP and DBP among non-BP medication users. These findings suggest changes in both respiratory effort and oxygenation during sleep influence BP.

INTRODUCTION

Hypertension is a prevalent risk factor for myocardial infarction and stroke.[1] Obstructive sleep apnoea (OSA) has been suggested as one of the contributing factors for high blood pressure (BP).[2] There are several mechanisms by which OSA could lead to heightened BP, including increased sympathetic activation and circulating catecholamines caused by intermittent hypoxia, hypercapnia, or sleep arousals.

Prior studies have shown that polysomnography (PSG) measurements, such as the apnoea–hypopnoea index (AHI), periodic limb movement index (PLMI) and reduced slow wave sleep (SWS), are associated with elevated BP.[34] However, the contribution of other OSA-induced abnormalities has not been well studied. Quantitative measures of sleep disturbance, airflow limitation and hypoxaemia have been identified, which could provide further insight into underlying OSA-related physiological mechanisms that cause hypertension.

The relation between sleep depth and OSA is complex.[5] Overt OSA reduces overall sleep depth because of frequent interruptions by obstructive events and arousals, and by excessive wake time that frequently accompanies OSA.[67] Poor quality sleep and excessive wake time have been independently associated with hypertension.[8] However, deep sleep promotes flow limitation which may lead to sustained hypercapnia and hypoxia which may increase BP.[9] A continuous index of sleep depth derived from electroencephalogram (EEG) termed the ‘odds ratio product’ (ORP) can distinguish between different levels of sleep depth within conventional sleep stages and has excellent correlation with arousability.[10] We also measured inspiratory flow limitation (IFL) and duty cycle (inspiratory time (T_i)/total respiratory cycle time (T_t)), two markers of airflow in the setting of higher upper airway resistance[1112] Third, we measured ‘hypoxic burden’, a recently described measurement that quantifies respiratory event-related hypoxaemia.[13] Compared with other measurements of sleep-related hypoxaemia, this index is specific to hypoxaemia resulting from obstructive events and captures the frequency, depth and duration of event-related breathing disturbances.

Using these unique measurements of sleep disturbances, we hypothesised (1) lower depth of sleep (as measured by ORP), (2) higher IFL and duty cycle and (3) higher hypoxic burden are each associated with higher BP among community-dwelling adults. We also examined whether these associations would be stronger among those with higher AHI, individuals not

using antihypertensive medication, and considered effect modification by cigarette smoking, which is a risk factor in cardiovascular disease and is associated with sleep-disordered breathing.[14,15]

METHODS

Study participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort of community-dwelling adults originally designed to investigate subclinical cardiovascular disease.[16] In all, 6814 adults between the ages of 45 and 84 years without clinically evident cardiovascular disease were enrolled from six US communities between 2000 and 2002. There were no criteria based on sleep and respiratory symptoms. Participants underwent follow-up visits including Exam 5 (2010–2012). Exam 5 participants were invited to participate in a sleep examination (2010–2013) which included completion of sleep questionnaires, actigraphy and PSG.[17] Institutional Review Board approval was obtained at all six study sites and Sleep Reading Centre and all participants provided written informed consent.

PSG and scoring

A 15-channel PSG monitor (Compumedics Somte System; Compumedics, Abbotsville, AU) collected the following: bilateral electrooculography, bipolar electrocardiography, chin electromyography, abdominal and thoracic respiratory inductance plethysmography, central, frontal and occipital EEG (sampled at 256 Hz), pulse oximetry, airflow (by thermocouple and nasal pressure transduction), and bilateral leg piezoelectric sensors.

Using standardised criteria, registered polysomnologists scored each sleep study at a centralised Sleep Reading Centre (Brigham and Women's Hospital, Boston, MA, USA) using approaches similar to those for the Sleep Heart Health Study.[18,19] The American Academy of Sleep Medicine scoring guidelines were used to score sleep stages and arousals.[20] Hypopnoeas were scored when the amplitude of the sum of the abdominal and thoracic inductance signals or the nasal pressure flow signal decreased by 30% or more for ≥10 s. Each event was linked to desaturation data. Apnoeas were scored when the thermocouple signal showed no respiratory deflections>10% baseline for greater than 10 s. Events were classified as either 'central' or 'obstructive' according to the presence or absence of respiratory effort. AHI was calculated based on the average number of all apnoeas and hypopnoeas associated with a 4% desaturation per hour of sleep. Periodic limb movements were identified by the pattern and number of limb movements (greater than four movements each separated by 5–90 s). The PLMI was the ratio of all periodic limb movements divided by sleep time. Scorers reliability was monitored regularly over time, inter-class and intra-class coefficients were high for all key parameters (eg, PLMI: 0.93–0.98; arousal index: 0.84–0.99; and AHI: 0.96–0.98).

Sleep disturbance exposure measurements

The ORP was measured using previously described methods.[10] Each 3 s epoch from the EEG was assigned a four-digit number, from 0000 to 9999 (bin number) representing from left to right the ranks of delta, theta, alpha-sigma and beta spectral power. For each bin

number, probability of being awake was determined from a look-up table constructed in development files from the number of epochs with the specific bin number occurring during arousals or in epochs scored wake divided by the total number of epochs with the same bin number in the entire development set. The probability of being 'awake' for each of the 10 000 bin numbers was listed in a look-up table. The probability was then divided by 40 producing a range from 0 (always asleep) to 2.5 (always awake). The reason to divide by 40 was because 40% of all epochs were 'awake' epochs in the development files, as this ratio is the ORP. Average ORP was obtained for the whole night and separately for non-rapid eye movement (NREM) and rapid eye movement (REM) sleep.

Duty cycle and IFL were determined from the nasal pressure signal. The flow signal was high-pass filtered to determine zero flow. Points of zero flow crossing were used to determine inspiratory and expiratory times when the signal was of adequate quality. Duty cycle was calculated from inspiratory time divided by the total respiratory cycle time (T_I/T_{tot}). IFL was identified by commercial software for scoring PSGs (Micele Sleep Scoring, Cerebra Health, Winnipeg, Canada). The algorithm was developed using results of a model that utilises known patterns of respiratory motor output during inspiration and the known range of respiratory resistance and compliance in individuals without upper airway obstruction. The model generated the full range of possible flow patterns when resistance does not increase as a function of increasing pressure output during the inspiratory phase. Deviations from these patterns indicated that resistance increased as inspiratory time and effort progressed, which is the hallmark of flow limitation. Apart from the commonly appreciated plateau in inspiratory flow, flow limitation is present when peak flow occurs very early in inspiration and then declines or it occurs very late in inspiration. Flow limitation was expressed as % of breaths with flow limitation.[21] Measurements were made over the entire night and in NREM and REM sleep.

The hypoxic burden is defined as the total area under the respiratory event-related desaturation cure, as described before.[13] The overall hypoxic burden captures the total amount of respiratory event-related hypoxaemia during a sleep period. The hypoxic burden is defined as the total area under the respiratory event-related desaturation curve.[13] For each scored respiratory event, regardless of oxygen desaturation or arousal, a pre-event baseline was determined, and the area under baseline-subtracted oxygen desaturation was calculated during a subject-specific search window. The sum of individual desaturation areas was divided by the sleep duration as the units of hypoxic burden are (%·min)/hour. Similar to overall hypoxic burden, which was calculated during a participant-specific search window, hypoxic burden in NREM and REM sleep was calculated during participant-specific search windows obtained separately from NREM and REM. The algorithm was implemented in MATLAB (The MathWorks, Natick, MA, USA).

BP measurements

Participants underwent resting BP measurements at Exam 5 in a seated position three times using an automated device. The average of the second and third BP measurements were used to calculate the systolic BP (SBP) and diastolic BP (DBP). To take into account hypertension medication use, SBP and DBP were adjusted by adding 10 mm Hg and 5 mm

Hg, respectively, among antihypertensive medication users.[22] Hypertension was defined as measured SBP ≥130 mm Hg, DBP ≥80 mm Hg and/or use of antihypertensive medication.[23]

Statistical analysis

Our primary outcome variables were SBP and DBP values adjusted for hypertension medication use. We used generalised linear models to examine associations of sleep disturbance exposure variables with BP. We used the identity link function and a Gaussian family for our generalised linear models. We used causal diagrams to identify potential confounders in addition to adjusting for other sleep parameters associated with BP and our exposure of interest a priori (eg, PLMI) (online supplementary figure S1).[32425] Models were adjusted for age, sex, race/ethnicity, smoking status, cigarette pack-years, current alcohol use, education status, body mass index (BMI, kg/m^2) and average PLMI. In order to evaluate the association of each sleep disturbance exposure with BP, we also adjusted each model for alternative physiological disturbances. For example, for our ORP exposure model, we adjusted for hypoxic burden and duty cycle. Collinearity was evaluated by the variance inflation factor (VIF). All covariates had VIF <5.0 in our models. Because IFL occurs in higher proportion during SWS, we also adjusted for time spent in N3 in our IFL models.

We stratified adjusted models by pre-specified variables including smoking status, OSA severity (normal: AHI<5; mild: 5≤AHI<15; moderate to severe: AHI≥15), and hypertension medication use and tested for interactions using likelihood ratio tests. We used SBP and DBP unadjusted for medication use as our dependent variables for our hypertension medication stratified analysis. Outcome variables were log-transformed to fulfil normality assumptions for our regression models. Participants with missing covariate data were excluded from analyses. Outcomes are reported per 1 SD increment of the natural log-transformed sleep disturbance exposure variable. SAS V9.4 (SAS Institute) was used to perform analyses.

RESULTS

Baseline characteristics

PSG data and Exam 5 BP measurements were available for 2055 MESA participants (online supplementary figure S2). Due to inadequate PSG signals we excluded 255, 208 and 218 studies from the 2055 available PSGs for the ORP (n=1800), NREM duty cycle/IFL (n=1847) and hypoxic burden (n=1837) analyses, respectively. Baseline characteristics of the entire cohort are summarised in table 1 and were not different from cohorts with valid ORP, duty cycle, IFL and hypoxic burden measurements. Baseline characteristics stratified by ORP, NREM duty cycle and hypoxic burden quartiles are shown in online supplementary tables S1, S2 and S3.

Associations of ORP, IFL and duty cycle with BP

A higher ORP was not significantly associated with SBP or DBP in unadjusted or adjusted models (table 2) or when calculated for NREM and REM ORP separately (online supplementary table S4). However, in analyses stratified by OSA severity, higher REM ORP was more strongly (and negatively) associated with SBP among those with mild

OSA compared with those with moderate-to-severe or no OSA (p value for OSA severity interaction=0.03; online supplementary table S5). Among those with mild OSA, each 1 SD increment in log-transformed REM ORP was associated with a 1.8% decrease in SBP (95% CI: 0.6 to 3.0, p=0.003).

A higher NREM IFL was associated with a lower SBP after adjusting for baseline covariates and per cent time in SWS: for every 1 SD increment in log-transformed NREM IFL there was a 0.8% decrease in SBP (95% CI: 0.1 to 1.5, p=0.04) (table 3). This association remained significant after adjusting for hypoxic burden and sleep depth (table 3). A higher NREM IFL was associated with a lower DBP after adjusting for baseline covariates, hypoxia and sleep depth: for every 1 SD increment in log-transformed NREM IFL there was a 0.8% decrease in DBP (95% CI: 0.1 to 1.4, p=0.02) (table 3). REM IFL was not associated with SBP and DBP after covariate adjustment.

A higher NREM duty cycle was associated with a lower SBP after adjusting for baseline covariates (Model 1): for every 1 SD increment in log-transformed NREM duty cycle, there was a 0.9% decrease in SBP (95% CI: 0.2 to 1.6, p=0.01) (table 4). This association remained significant after adjusting for hypoxic burden and sleep depth (table 4). Similarly, a higher REM duty cycle was associated with lower SBP (Model 1): for every 1 SD increment in log-transformed REM duty cycle, there was a 0.9% decrease in SBP (95% CI: 0.2 to 1.7, p=0.002) (table 4). There were no significant associations of NREM or REM duty cycle with DBP.

Inverse associations of NREM and REM duty cycle with SBP and DBP were each stronger among those with mild OSA compared with those without OSA and moderate-to-severe OSA (all p values for OSA severity interaction ≤0.03, online supplementary table S5). The association between NREM duty cycle and DBP was stronger among never smokers compared with ever smokers (p=0.007 for smoking interaction, online supplementary table S6). A stronger (negative) association was observed between REM duty cycle with both SBP and DBP in never smokers compared with ever smokers (all p values≤0.03 for smoking interaction, online supplementary table S6).

Associations between hypoxic burden and BP

A higher overall hypoxic burden was associated with a higher DBP after adjusting for baseline covariates: for every 1 SD increment in log-transformed hypoxic burden there was a 0.9% increase in DBP (95% CI: 0.3 to 1.6, p=0.004) (table 5). This association remained significant after adjusting for sleep depth and duty cycle (table 5). We found similar findings with hypoxic burden and DBP in both NREM and REM sleep (table 5). Hypoxic burden was not significantly associated with SBP in adjusted models. The associations of overall hypoxic burden with SBP and DBP were stronger among those not taking antihypertensive medications compared with medication users (all p values for medication interaction ≤0.03, online supplementary table S7). Among non-medication users, for every 1 SD increment in log-transformed hypoxic burden there was a 1.1% (95% CI: 0.1 to 2.1, p=0.03) and a 1.9% increase (95% CI: 1.0 to 2.8, p<0.001) in SBP and DBP, respectively. In REM, higher hypoxic burden was associated with higher SBP among those with mild OSA (p value for OSA severity interaction=0.03. online supplementary table S5) and with higher DBP

among never smokers (p value for smoking interaction=0.02) (online supplementary table S6). Higher NREM hypoxic burden was associated with higher SBP and both NREM and REM hypoxic burden were each associated with higher DBP among non-medication users (all p values for medication interaction ≤0.04, online supplementary table S7).

DISCUSSION

In our systematic analysis of novel metrics defining three pathways describing sleep disturbances: sleep depth, airflow limitation and hypoxia, we found that only increased hypoxic burden was associated with increased DBP overall and SBP and DBP among non-hypertension medication users. Unexpectedly, higher IFL and duty cycle in NREM sleep were associated with lower SBP. Stratified analyses suggested that the associations between duty cycle and BP varied by smoking status and OSA severity. There was no association observed between a quantitative EEG index of sleep depth and BP. Overall, these findings support prior studies linking sleep apnoea-associated hypoxia to the risk of hypertension.[26]

More traditional measures of evaluating hypoxia during sleep, such as the oxygen desaturation index, and their association with BP have been investigated.[27] However, they rely on arbitrary thresholds that do not quantify the severity of hypoxaemia and are not specific to OSA. The hypoxic burden, a respiratory event-specific measure, was associated with small but significant increases in DBP overall and SBP and DBP among those not using BP medications. Intermittent hypoxia can contribute to hypertension by altering sympathetic and parasympathetic activation leading to a surge in catecholamine levels and promotion of inflammation through generation of reactive oxygen species and inflammatory cytokines.[2829] In the overall cohort, findings were similar for NREM and REM sleep, which differs from prior studies that reported a stronger association between AHI and hypertension in REM.[3031] A key distinction between AHI in REM versus NREM is that AHI values in REM typically include events which are longer and associated with more hypoxaemia than events included in the NREM AHI. The inclusion of many events with mild desaturation may reduce the predictive value of the NREM AHI. In contrast, direct estimation of hypoxic burden across sleep states characterises between-individual variability in levels of hypoxaemia, which is not captured by AHI but may be a key driver of vascular disease.

IFL may provide further mechanistic data linking OSA to hypertension.[1221] IFL indicates high upper airway resistance occurring in the absence of evident hypopnoeas and without hypoxaemia. Changes in intrathoracic pressure related to IFL and subsequent stimulation of the neurohormonal system and leftward shifts of the interventricular septum may lead to abnormal cardiac remodelling and worsen endothelial function.[3233] Periods of IFL are usually terminated by arousals which may contribute to acute elevations in BP through sympathetic activation.[32] Another metric associated with increased flow limitation is duty cycle. Higher inspiratory resistance leads to obstructed ventilation, which is compensated for by a higher duty cycle.[511] Duty cycle has the advantage over flow limitation in that the increase in duty cycle only occurs when effort increases and intrathoracic pressure decreases.[3435] Thus, an increase in duty cycle is a marker of flow limitation with associated increased effort.

While we hypothesised that metrics of increased inspiratory resistance (IFL, duty cycle) would be associated with higher BP, we found the opposite. There are several potential explanations for this. There were significant negative correlations between these high resistance indices and other variables, including BMI. Although we adjusted for BMI and other covariates, it is possible that residual confounding may have obscured true associations. SWS is characterised by both increased flow limitation (with few apnoeas) and reduced sympathetic tone; therefore, confounding due to SWS could potentially explain an association between IFL and lower BP. While no appreciable differences were observed after adjusting for SWS measured during PSG, it is possible that SWS was not adequately measured during a single night study. Otherwise, it is possible that the unique pattern of increased left ventricular afterload due to greater IFL, consisting of a load increase during only part of the breath and occurring only during part of the day (sleep time) may result in favourable cardiac and peripheral vascular changes. This may result in lower BP when there is no increased load (during wakefulness), and that such effects may be pronounced in older individuals. Duty cycle is an arousal-independent ventilatory mechanism during sleep, as the ability to maintain ventilation without invoking arousals may lead to less sympathetic nervous system activation and catecholamine release.[11] Studies during wakefulness also suggest that increasing inspiratory effort or duty cycle can cause reflex reductions in sympathetic nerve activity through pulmonary artery stretch receptor activation.[36] These sympathoinhibitory reflexes are further modulated by baseline lung volumes and parasympathetic activity, which may be higher in NREM compared with REM sleep, and thus may explain why we observed stronger negative associations of IFL and duty cycle with BP in NREM sleep and with mild OSA.[37] The extent to which sympathoinhibitory mechanisms operate during sleep during periods of upper airway obstruction is, however, unclear; in fact, ventilatory and mechanoreceptor responses to upper airway obstruction during sleep may vary considerably across individuals. Experimental studies are needed to address the underlying mechanisms explaining the negative associations between IFL and duty cycle with BP.

We observed that the inverse associations between duty cycle and BP were stronger among those with mild OSA, suggesting that the protective effect of upper airway resistance loading is attenuated in the presence of moderate or severe OSA. While snoring, which reflects IFL, has been associated with hypertension, prior research has not eliminated the contribution of hypopnoeas and hypoxaemia to elevations in BP.[38] Regardless of the mechanism driving the negative association between sustained high resistance and BP, our findings do not support an adverse effect of IFL without apnoeas on BP and highlight the complex interplay between respiration and vascular function.

We observed stronger negative associations of REM duty cycle with SBP and REM and NREM duty cycle with DBP among never smokers. These observations could be driven by differences in lung function leading to worsening ventilation in smokers. Cigarette exposure may contribute to an impaired ventilatory response to higher upper airway loading as suggested by a study that showed greater time spent with an oxygen saturation below 90% during sleep among current smokers versus never smokers.[39] The significance of our findings is uncertain as they are derived from secondary analysis.

We expected that participants with higher ORP, which increases with excessive wake time and/or fragmented sleep, would have higher BP. The lack of positive association between ORP and BP is surprising given the strong positive associations of ORP with AHI and hypoxic burden. A hypertension-promoting variable might have been preferentially operative in subjects with deeper sleep that we did not account for. Our cohort consisted of older adults who typically have less SWS and more frequent awakenings.[40] Therefore, worsening sleep depth may not influence BP in older adults in whom sleep microarchitecture is disturbed due to multiple factors. REM ORP was associated with lower SBP among those with mild OSA in a stratified analysis but should be interpreted with caution. Studies that further our understanding of the inter-relationship of sleep microarchitecture with BP may be informative.

Our study has several strengths and limitations. To our knowledge, this is the first study to examine the associations of a set of sleep disturbance measures selected to quantify potential sleep-disordered breathing-related stressors with BP. We analysed data from a large, racially and ethnically diverse community-based cohort, although an older group which may limit the study's generalisability. The cross-sectional design limits our ability to interpret the temporality of the observed associations. We accounted for antihypertensive medication use in our analysis using previously validated methods and associations were not significantly modified by antihypertension medication use for most of the sleep parameters we examined (p value for interaction ≥0.06).[22] Also, associations between sleep parameters and BP in non-users were largely in the same direction as the overall cohort (online supplementary table S7). However, we cannot rule out that the frequent use of medication may have obscured some associations due to the impact of antihypertensive medication on sleep outcomes, or because adjustment for BP medications did not adequately model participant's untreated BP profile. This is an important limitation as longitudinal studies with a larger cohort will be informative. Our main outcome of BP was measured only during the participant's exam visit at daytime. Ambulatory and nocturnal BPs might provide further insight into the potential mechanisms driving our findings. There may have been changes to BP medication use between Exam 5 BP measurements and when the sleep study was performed which we could not account for. Although we adjusted for several covariates, there may still be residual confounding.

In conclusion, we found that a higher burden of hypoxia was associated with higher BP while a higher duty cycle and IFL were associated with lower BP among community-dwelling adults. Among older adults, a quantitative measure of sleep depth was not associated with BP. Our findings suggest that an individual's ability to maintain ventilation under increased upper airway resistance may attenuate BP elevations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests

AA has received personal fees from Somnifx and Apnimed. MY has received personal fees from Cerebra Health. MY has patent for method and software to determine quality of sleep and wakefulness. MY has patent for method and apparatus for arousal intensity scoring. SSR has received grants and personal fees from Jazz Pharma. SSR has received personal fees from Respircardia.

Data availability statement

Data are available upon reasonable request.

REFERENCES

1. Muntner P, Carey RM, Gidding S, et al. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. Circulation2018;137:109–18. [PubMed: 29133599]
2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med2002;165:1217–39. [PubMed: 11991871]
3. Dean DA, Wang R, Jacobs DR, et al. A systematic assessment of the association of polysomnographic indices with blood pressure: the multi-ethnic study of atherosclerosis (MESA). Sleep2015;38:587–96. [PubMed: 25348124]
4. Javaheri S, Zhao YY, Punjabi NM, et al. Slow-Wave sleep is associated with incident hypertension: the sleep heart health study. Sleep2018;41:1.
5. Younes MContributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. Am J Respir Crit Care Med2003;168:645–58. [PubMed: 12773321]
6. Redline S, Kirchner HL, Quan SF, et al. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. Arch Intern Med2004;164:406–18. [PubMed: 14980992]
7. Mediano O, Barceló A, de la Peña M, et al. Daytime sleepiness and polysomnographic variables in sleep apnoea patients. Rev Port Pneumol2007;13:896–8. [PubMed: 25977182]
8. Khan MS, Aouad R. The effects of insomnia and sleep loss on cardiovascular disease. Sleep Med Clin2017;12:167–77. [PubMed: 28477772]
9. Rimpilä V, Saaresranta T, Huhtala H, et al. Transcutaneous CO(2) plateau as set-point for respiratory drive during upper airway flow-limitation. Respir Physiol Neurobiol2014;191:44–51. [PubMed: 24200642]
10. Younes M, Ostrowski M, Soiferman M, et al. Odds ratio product of sleep EEG as a continuous measure of sleep state. Sleep2015;38:641–54. [PubMed: 25348125]
11. Younes MRole of respiratory control mechanisms in the pathogenesis of obstructive sleep disorders. J Appl Physiol2008;105:1389–405. [PubMed: 18787092]
12. Arora N, Meskill G, Guilleminault C. The role of flow limitation as an important diagnostic tool and clinical finding in mild sleep-disordered breathing. Sleep Sci2015;8:134–42. [PubMed: 26779320]

13. Azarbarzin A, Sands SA, Stone KL, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the osteoporotic fractures in men study and the sleep heart health study. Eur Heart J2019;40:1149–57. [PubMed: 30376054]
14. Wetter DW, Young TB, Bidwell TR, et al. Smoking as a risk factor for sleep-disordered breathing. Arch Intern Med1994;154:2219–24. [PubMed: 7944843]
15. Hackshaw A, Morris JK, Boniface S, et al. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ2018;360.
16. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic study of atherosclerosis: objectives and design. Am J Epidemiol2002;156:871–81. [PubMed: 12397006]
17. Chen X, Wang R, Zee P, et al. Racial/Ethnic differences in sleep disturbances: the multi-ethnic study of atherosclerosis (MESA). Sleep2015;38:877–88. [PubMed: 25409106]
18. Redline S, Sanders MH, Lind BK, et al. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. sleep heart health research Group. Sleep1998;21:759–67. [PubMed: 11300121]
19. Whitney CW, Gottlieb DJ, Redline S, et al. Reliability of scoring respiratory disturbance indices and sleep staging. Sleep1998;21:749–57. [PubMed: 11286351]
20. Iber CAmerican Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events : rules, terminology, and technical specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.
21. Sabil A, Eberhard A, Baconnier P, et al. A physical model of inspiratory flow limitation in awake healthy subjects. Adv Exp Med Biol2004;551:211–6. [PubMed: 15602966]
22. Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature2011;478:103–9. [PubMed: 21909115]
23. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines. J Am Coll Cardiol2018;71:e127–248. [PubMed: 29146535]
24. Lederer DJ, Bell SC, Branson RD, et al. Control of confounding and reporting of results in causal inference studies. guidance for authors from editors of respiratory, sleep, and critical care journals. Ann Am Thorac Soc2019;16:22–8. [PubMed: 30230362]
25. Textor J, van der Zander B, Gilthorpe MS, et al. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol2016;45:1887–94. [PubMed: 28089956]
26. Turnbull CD, Sen D, Kohler M, et al. Effect of supplemental oxygen on blood pressure in obstructive sleep apnea (SOX). A randomized continuous positive airway pressure withdrawal trial. Am J Respir Crit Care Med2019;199:211–9. [PubMed: 30025470]
27. Pankow W, Nabe B, Lies A, et al. Influence of sleep apnea on 24-hour blood pressure. Chest1997;112:1253–8. [PubMed: 9367465]
28. Yamauchi M, Nakano H, Maekawa J, et al. Oxidative stress in obstructive sleep apnea. Chest2005;127:1674–9. [PubMed: 15888845]
29. Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. Mayo Clin Proc2009;84:822–30. [PubMed: 19720780]
30. Appleton SL, Vakulin A, Martin SA, et al. Hypertension is associated with undiagnosed OSA during rapid eye movement sleep. Chest2016;150:495–505. [PubMed: 27001264]
31. Mokhlesi B, Finn LA, Hagen EW, et al. Obstructive sleep apnea during REM sleep and hypertension. Results of the Wisconsin sleep cohort. Am J Respir Crit Care Med2014;190:1158–67. [PubMed: 25295854]
32. Guilleminault C, Stoohs R, Shiomi T, et al. Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension. Chest1996;109:901–8. [PubMed: 8635368]
33. Shiomi T, Guilleminault C, Stoohs R, et al. Leftward shift of the interventricular septum and pulsus paradoxus in obstructive sleep apnea syndrome. Chest1991;100:894–902. [PubMed: 1914603]
34. Hosselet JJ, Norman RG, Ayappa I, et al. Detection of flow limitation with a nasal cannula/pressure transducer system. Am J Respir Crit Care Med1998;157:1461–7. [PubMed: 9603124]

35. Stoohs R, Guilleminault C. Snoring during NREM sleep: respiratory timing, esophageal pressure and EEG arousal. Respir Physiol1991;85:151–67. [PubMed: 1947456]

36. Seals DR, Suwarno NO, Dempsey JA. Influence of lung volume on sympathetic nerve discharge in normal humans. Circ Res1990;67:130–41. [PubMed: 2364488]

37. Trinder J, Kleiman J, Carrington M, et al. Autonomic activity during human sleep as a function of time and sleep stage. J Sleep Res2001;10:253–64. [PubMed: 11903855]

38. Bixler EO, Vgontzas AN, Lin HM, et al. Association of hypertension and sleep-disordered breathing. Arch Intern Med2000;160:2289–95. [PubMed: 10927725]

39. Conway SG, Roizenblatt SS, Palombini L, et al. Effect of smoking habits on sleep. Braz J Med Biol Res2008;41:722–7. [PubMed: 18797708]

40. Feinberg I, Koresko RL, Heller N. Eeg sleep patterns as a function of normal and pathological aging in man. J Psychiatr Res1967;5:107–44. [PubMed: 6056816]

Key messages

What is the key question?

- Can novel measurements of sleep depth, airflow and hypoxia from polysomnography provide more insight into the role of sleep-disordered breathing in blood pressure (BP)?

What is the bottom line?

- A greater burden of hypoxia related to obstruction was associated with higher BP among community-dwelling adults not using antihypertensive medications while markers of airflow were associated with lower BP overall.

Why read on?

- Our study suggests the ability to maintain ventilation in the setting of increased upper airway resistance may blunt BP elevations.

Table 1

Baseline characteristics of the Multi-Ethnic Study of Atherosclerosis sleep cohort

Participants, n	2055
Age, years	68.4 (9.1)
Female, %	54%
Race/ethnicity, %	
White	36%
Asian	12%
Black	28%
Hispanic	24%
Systolic blood pressure, mm Hg *	128.2 (21.8)
Diastolic blood pressure, mm Hg *	70.9 (10.1)
Hypertension, %	53%
Height, cm	165.4 (10.1)
Waist, cm	99.4 (14.4)
Body mass index, kg/m^2	28.7 (5.5)
Blood pressure medication use, %	53%
Ever smoker, %	53%
Diabetes, %	20%
Spirometry †	
Forced expiratory volume at 1 s (FEV_1, L/s)	2.3 (0.7)
Percent predicted FEV_1	95.2% (19.1)
Forced vital capacity (FVC, L)	3.1 (0.9)
Per cent predicted FVC	96.8% (17.4)
AHI, events/hour	14.8 (16.7)
AHI<5 events/hour	34%
5<AHI < 15 events/hour	32%
AHI>15 events/hour	34%
Overall ORP	1.3 (0.3)
NREM ORP	1.0 (0.3)
REM ORP	1.5 (0.4)
IFL, % of breaths with flow limitation	
NREM IFL	29.8 (15.8)
REM IFL	36.9 (15.7)
Duty cycle, T_I/T_{tot}	
NREM duty cycle	0.4 (0.1)
REM duty cycle	0.4 (0.1)
Hypoxic burden, (% min)/hour	31.2 (41.7)

Data presented as mean±SD for continuous variables and (%) for categorical variables.

* Exam 5 blood pressure measurements unadjusted for medication use.

† A subset of participants underwent spirometry at Exam 5 (n=1506).

AHI, apnoea–hypopnoea index; IFL, inspiratory flow limitation; NREM, non-rapid eye movement; ORP, odds ratio product; REM, rapid eye movement.

Table 2

Association of overall ORP with SBP and DBP

	% Change in SBP (95% CI)*	P value	% Change in DBP (95% CI)*	P value
Unadjusted model (n=1799)	0.7 (−0.1 to 1.4)	0.09	0.2 (−0.5 to 0.8)	0.56
Model 1 (n=1765)	0.3 (−0.4 to 1.0)	0.48	0.3 (−0.3 to 0.9)	0.39
Model 2 (n=1754)	0.2 (−0.5 to 1.0)	0.51	0.2 (−0.4 to 0.8)	0.51
Model 3 (n=1754)	0.3 (−0.5 to 1.0)	0.49	0.2 (−0.4 to 0.9)	0.50

Model 1: Adjusted for age, sex, race/ethnicity, body mass index (kg/m^2), smoking status, cigarette pack-years, alcohol use, periodic limb movement, education level.

Model 2: Model 1+hypoxic burden ((%·min)/hour).

Model 3: Model 2+duty cycle.

*All results reported per SD increment of natural log-transformed ORP.

DBP, diastolic blood pressure; ORP, odds ratio product; SBP, systolic blood pressure.

Table 3

Associations of NREM and REM IFL with SBP and DBP

	% Change in SBP (95% CI)*	P value	% Change in DBP (95% CI)*	P value
NREM IFL				
Unadjusted model (n=1847)	−1.5 (−2.3 to −0.8)	<0.001	−0.6 (−1.2 to 0.04)	0.06
Model 1 (n=1813)	−0.8 (−1.5 to −0.1)	0.04	−0.6 (−1.2 to 0.07)	0.08
Model 2 (n=1802)	−0.8 (−1.5 to −0.1)	0.03	−0.7 (−1.3 to −0.1)	0.03
Model 3 (n=1754)	−0.8 (−1.6 to −0.1)	0.02	−0.8 (−1.4 to −0.1)	0.02
REM IFL				
Unadjusted model (n=1811)	−0.9 (−1.7 to −0.2)	0.02	−0.1 (−0.7 to 0.5)	0.76
Model 1 (n=1778)	−0.3 (−1.0 to 0.4)	0.41	−0.2 (−0.8 to 0.5)	0.60
Model 2 (n=1767)	−0.3 (−1.0 to 0.4)	0.36	−0.2 (−0.8 to 0.4)	0.50
Model 3 (n=1713)	−0.2 (−0.9 to 0.6)	0.60	−0.1 (−0.7 to 0.6)	0.78

Model 1: Adjusted for age, sex, race/ethnicity, body mass index (kg/m^2), smoking status, cigarette pack-years, alcohol use, periodic limb movement, education level, % of time spent in N3 and N4 sleep.

Model 2: Model 1+hypoxic burden ((%·min)/hour).

Model 3: Model 2+ odds ratio product.

*All results reported per SD increment of natural log-transformed NREM and REM IFL.

DBP, diastolic blood pressure; IFL, inspiratory flow limitation; NREM, non-rapid eye movement; REM, rapid eye movement;SBP, systolic blood pressure.

Table 4

Associations of NREM and REM duty cycle with SBP and DBP

	% Change in SBP (95% CI)*	Pvalue	% Change in DBP (95% CI)*	P value
NREM duty cycle				
Unadjusted model (n=1847)	−1.7 (−2.5 to −1.0)	<0.001	−0.1 (−0.7 to 0.6)	0.86
Model 1 (n=1813)	−0.9 (−1.6 to −0.2)	0.01	−0.5 (−1.2 to 0.1)	0.10
Model 2 (n=1802)	−0.9 (−1.6 to −0.2)	0.02	−0.5 (−1.1 to 0.1)	0.11
Model 3 (n=1754)	−0.9 (−1.6 to −0.1)	0.02	−0.6 (−1.2 to 0.1)	0.09
REM duty cycle				
Unadjusted model (n=1811)	−1.8 (−2.6 to −1.1)	<0.001	0.1 (−0.5 to 0.8)	0.75
Model 1 (n=1778)	−0.9 (−1.7 to −0.2)	0.002	−0.3 (−1.0 to 0.3)	0.30
Model 2 (n=1767)	−0.9 (−1.6 to −0.1)	0.02	−0.2 (−0.8 to 0.4)	0.54
Model 3 (n=1713)	−0.7 (−1.4 to 0.1)	0.07	−0.1 (−0.8 to 0.5)	0.69

Model 1: Adjusted for age, sex, race/ethnicity, body mass index (kg/m^2), smoking status, cigarette pack-years, alcohol use, periodic limb movement, education level.

Model 2: Model 1+hypoxic burden ((%·min)/hour).

Model 3: Model 2+odds ratio product.

*All results reported per SD increment of natural log-transformed NREM and REM duty cycle.

DBP, diastolic blood pressure; NREM, non-rapid eye movement; REM, rapid eye movement;SBP, systolic blood pressure.

Table 5

Association of hypoxic burden with SBP and DBP

	% Change in SBP (95% CI)*	p-value	% Change in DBP (95% CI)*	P value
Overall hypoxic burden				
Unadjusted model (n=2047)	1.5 (0.8 to 2.2)	<0.001	1.6 (1.0 to 2.2)	<0.001
Model 1 (n=2013)	0.5 (−0.3 to 1.2)	0.21	0.9 (0.3 to 1.6)	0.004
Model 2 (n=1761)	0.5 (−0.3 to 1.3)	0.21	1.1 (0.3 to 1.6)	0.002
Model 3 (n=1761)	0.5 (−0.3 to 1.3)	0.21	1.1 (0.4 to 1.8)	0.002
NREM hypoxic burden				
Unadjusted model (n=2036)	1.2 (0.5 to 1.9)	<0.001	1.6 (1.0 to 2.2)	<0.001
Model 1 (n=2002)	0.4 (−0.3 to 1.2)	0.26	0.9 (0.2 to 1.6)	0.007
Model 2 (n=1750)	0.4 (−0.4 to 1.2)	0.34	1.0 (0.3 to 1.8)	0.006
Model 3 (n=1750)	0.4 (−0.4 to 1.2)	0.31	1.0 (0.3 to 1.8)	0.005
REM hypoxic burden				
Unadjusted model (n=1991)	1.7 (0.9 to 2.4)	<0.001	1.1 (0.5 to 1.8)	<0.001
Model 1 (n=1957)	0.7 (−0.005 to 1.5)	0.051	0.8 (0.2 to 1.4)	0.02
Model 2 (n=1717)	0.6 (−0.2 to 1.4)	0.13	0.8 (0.1 to 1.5)	0.03
Model 3 (n=1713)	0.5 (−0.3 to 1.3)	0.25	0.7 (0.02 to 1.4)	0.04

Model 1: Adjusted for age, sex, race/ethnicity, body mass index (kg/m^2), smoking status, cigarette pack-years, alcohol use, periodic limb movement, education level.

Model 2: Model 1+odds ratio product.

Model 3: Model 2+duty cycle.

*All results reported per SD increment of natural log-transformed hypoxic burden.

DBP, diastolic blood pressure; NREM, non-rapid eye movement; REM, rapid eye movement; SBP, systolic blood pressure.