Adverse Impact of Sleep Restriction and Circadian Misalignment on Autonomic Function in Healthy Young Adults

Abstract
Insufficient sleep and circadian rhythm disturbances have been each associated with adverse cardiovascular outcomes in epidemiological studies, but experimental evidence for a causal link is scarce. The present study compares the impact of circadian misalignment (CM) to circadian alignment (CA) on human autonomic function using a nonrandomized parallel group design to achieve the same total sleep time in both conditions. After baseline assessments (3 days with 10-hour bedtimes), 26 healthy young adults were assigned to sleep restriction (SR; eight 5-hour bedtimes), with either fixed nocturnal bedtimes (CA; n=13) or bedtimes delayed by 8.5 hours on 4 of the 8 days (CM; n=13). Daytime ambulatory blood pressure and heart rate (HR; CA, n=11; CM, n=10) and 24-hour urinary norepinephrine levels (CA, n=13; CM, n=13) were assessed at baseline and at the end of SR. Nocturnal HR and HR variability were analyzed during sleep at baseline and during the fourth and seventh nights of SR (CA, n=8; CM, n=12). SR resulted in a significant increase in daytime HR in both groups, without changes in blood pressure. SR increased 24-hour urinary norepinephrine in the CM group (30±4 versus 21±2 μg), but not in the CA group (group×condition; P=0.005). In contrast to the lack of detectable impact of CM on daytime autonomic function, SR with CM elicited greater increases in nocturnal HR, as well as greater reductions in vagal indices of HR variability, than SR without CM (group×condition; P<0.05). In conclusion, SR and CM both result in impaired autonomic function that could lead, under chronic conditions, to enhanced cardiovascular risk.

Role of the Gut Microbiome in Obstructive Sleep Apnea–Induced Hypertension

Abstract
Individuals having obstructive sleep apnea (OSA) are at increased risk for systemic hypertension. The importance of a healthy gut microbiota, and detriment of a dysbiotic microbiota, on host physiology is becoming increasingly evident. We tested the hypothesis that gut dysbiosis contributes to hypertension observed with OSA. OSA was modeled in rats by inflating a tracheal balloon during the sleep cycle (10-s inflations, 60 per hour). On normal chow diet, OSA had no effect on blood pressure; however, in rats fed a high-fat diet, blood pressure increased 24 and 29 mm Hg after 7 and 14 days of OSA, respectively (P<0.05 each). Bacterial community characterization was performed on fecal pellets isolated before and after 14 days of OSA in chow- and high-fat–fed rats. High-fat diet and OSA led to significant alterations of the gut microbiota, including decreases in bacterial taxa known to produce the short chain fatty acid butyrate (P<0.05). Finally, transplant of dysbiotic cecal contents from hypertensive OSA rats on high-fat diet into OSA-recipient rats on normal chow diet (shown to be normotensive) resulted in hypertension similar to that of the donor (increased 14 and 32 mm Hg after 7 and 14 days of OSA, respectively; P<0.05). These studies demonstrate a causal relationship between gut dysbiosis and hypertension and suggest that manipulation of the microbiota may be a viable treatment for OSA-induced, and possibly other forms of, hypertension.
**Glucocorticoids Induce Nondipping Blood Pressure by Activating the Thiazide-Sensitive Cotransporter**

**Abstract**

Blood pressure (BP) normally dips during sleep, and nondipping increases cardiovascular risk. Hydrochlorothiazide restores the dipping BP profile in nondipping patients, suggesting that the NaCl cotransporter, NCC, is an important determinant of daily BP variation. NCC activity in cells is regulated by the circadian transcription factor per1. In vivo, circadian genes are entrained via the hypothalamic–pituitary–adrenal axis. Here, we test whether abnormal glucocorticoid rhythms impair NCC and induce nondipping. Nighttime dosing of thiazides may be particularly beneficial in patients with modest glucocorticoid excess.

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**Low-Salt Diet and Circadian Dysfunction Synergize to Induce Angiotensin II–Dependent Hypertension in Mice**

**Abstract**

Blood pressure exhibits a robust circadian rhythm in health. In hypertension, sleep apnea, and even shift work, this balanced rhythm is perturbed by elevations in nighttime blood pressure, inflicting silent damage to the vasculature and body organs. Herein, we examined the influence of circadian dysfunction during experimental hypertension in mice. Using radiotelemetry to measure ambulatory blood pressure and activity, the effects of angiotensin II administration were studied in wild-type and period isoform knockout (KO) mice (Per2-KO, Per2, 3-KO, and Per1, 2, 3-KO/Per triple KO mice). On a normal diet, administration of angiotensin II caused nondipping blood pressure and exacerbated vascular hypertrophy in the period isoform KO mice relative to wild-type mice. To study the endogenous effects of angiotensin II stimulation, we then administered a low-salt diet to the mice, which does stimulate endogenous angiotensin II in addition to lowering blood pressure. A low-salt diet decreased blood pressure in wild-type mice. In contrast, period isoform KO mice lost their circadian rhythm in blood pressure on a low-salt diet because of an increase in resting blood pressure, which was restorable to rhythmicity by the angiotensin receptor blocker losartan. Chronic administration of low salt caused vascular hypertrophy in period isoform KO mice, which also exhibited increased renin levels and altered angiotensin I receptor expression. These data suggest that circadian clock genes may act to inhibit or control renin/angiotensin signaling. Moreover, circadian disorders, such as sleep apnea and shift work, may alter the homeostatic responses to sodium restriction to potentially influence nocturnal hypertension.

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**Baroreflex Activation Therapy Lowers Arterial Pressure Without Apparent Stimulation of the Carotid Bodies**

**Abstract**

Carotid baroreflex activation therapy produces a sustained fall in blood pressure in patients with resistant hypertension. Because the activation electrodes are implanted at the level of the carotid sinus, it is conceivable that the nearby located carotid body chemoreceptors are stimulated as well. Physiological stimulation of the carotid chemoreceptors not only stimulates respiration but also increases sympathetic activity, which may counteract the effects of baroreflex activation. The aim of this exploratory study is to investigate whether there is concomitant carotid chemoreflex activation during baroreflex activation therapy. Fifteen participants with the Rheos system were included in this single-center study. At arrival at the clinic, the device was switched off for 2 hours while patients were at rest. Subsequently, the device was switched on at 6 electric settings of high and low frequencies and amplitudes. Respiration and blood pressure measurements were performed during all device activation settings. Multilevel statistical models were adjusted for age, sex, body mass index, antihypertensive therapeutic index, sleep apnea, coronary artery disease, systolic blood pressure, and heart rate. There was no change in end-tidal carbon dioxide, partial pressure of carbon dioxide, breath duration, and breathing frequency during any of the electric settings with the device. Nevertheless, mean arterial pressure showed a highly significant decrease during electric activation $(P<0.001)$. Carotid baroreflex activation therapy using the Rheos system did not stimulate respiration at several electric device activation energies, which suggests that there is no appreciable coactivation of carotid body chemoreceptors during device therapy.
Ethnic Differences in the Degree of Morning Blood Pressure Surge and in Its Determinants Between Japanese and European Hypertensive Subjects: Data From the ARTEMIS Study

Abstract

Morning blood pressure (BP) surge has been reported to be a prognostic factor for cardiovascular events. Its determinants are still poorly defined, however. In particular, it is not clear whether ethnic differences play a role in determining morning surge (MS) size. Aim of our study was to explore whether differences exist in the size of MS between Japanese and Western European hypertensive patients. We included 2887 untreated hypertensive patients (age 62.3±8.8 years) from a European ambulatory BP monitoring database and 811 hypertensive patients from a Japanese database (Jichi Medical School Ambulatory Blood Pressure Monitoring WAVE1, age 72.3±9.8 years) following the same inclusion criteria. Their 24-hour ambulatory BP monitoring recordings were analyzed focusing on MS. Sleep-trough MS was defined as the difference between mean systolic BP during the 2 hours after awakening and mean systolic BP during the 1-hour night period that included the lowest sleep BP level. The sleep-trough MS was higher in Japanese than in European hypertensive patients after adjusting for age and 24-hour mean BP levels (40.1 [95% confidence interval 39.0–41.2] versus 23.0 [22.4–23.5] mm Hg; P<0.001). This difference remained significant after accounting for differences in nighttime BP dipping. Age was independently associated with MS in the Japanese database, but not in the European subjects. Our results for the first time show the occurrence of substantial ethnic differences in the degree of MS. These findings may help in understanding the role of ethnic factors in cardiovascular risk assessment and in identifying possible ethnicity-related differences in the most effective measures to be implemented for prevention of BP-related cardiovascular events.

Age-Related Difference in the Sleep Pressure–Lowering Effect Between an Angiotensin II Receptor Blocker and a Calcium Channel Blocker in Asian Hypertensives: The ACS1 Study

Abstract

Sleep blood pressure (BP), which is partly determined by salt sensitivity and intake, is an important cardiovascular risk in hypertensives. However, there have been no studies on age-related differences in the sleep BP–lowering effect between angiotensin II receptor blockers and calcium channel blockers in Asians. Azilsartan Circadian and Sleep Pressure–the 1st Study was a multicenter, randomized, open-label, 2-parallel-group study conducted to compare the efficacy of 8-week oral treatment with an angiotensin II receptor blocker (azilsartan 20 mg) or a calcium channel blocker (amlodipine 5 mg) on sleep BP as evaluated by ambulatory BP monitoring. Among the overall population, amlodipine treatment achieved significantly greater reduction in sleep BP, awake BP, and 24-hour BP than azilsartan treatment. BP reduction by amlodipine was particularly pronounced in elderly hypertensive patients aged ≥60 years old. Among patients ≥60 years old, the amlodipine group had numerically, but not significantly, higher control rate of sleep BP compared with the azilsartan group. Similar results were found for awake BP and 24-hour BP. These results suggest a greater BP reduction/control by amlodipine compared with azilsartan and that reduction/control of BP by amlodipine was also more effective in the elderly population. As recommended in the American Society of Hypertension/The international Society of Hypertension and the National Institute for Health and Clinical Excellence guidelines for differentiating treatment according to age, amlodipine should be one of the options for starting treatment in the elderly population.

Periodic Limb Movements During Sleep and Prevalent Hypertension in the Multiethnic Study of Atherosclerosis

Abstract

Periodic limb movements during sleep (PLMS) are associated with immediate increases in blood pressure. Both PLMS and hypertension have different distributions across racial/ethnic groups. We sought to determine whether PLMS is associated with hypertension among various racial/ethnic groups. A total of 1740 men and women underwent measurement of blood pressure and polysomnography with quantification of PLMS. Hypertension was defined as systolic blood pressure (SBP) ≥140, diastolic BP ≥90, or taking antihypertensive medication. For those taking antihypertensives, an estimated pretreatment SBP value was derived based on observed SBP and medication type/dose. Measures of PLMS, PLMS index, and PLMS arousal index were the main explanatory variables. Hypertension and SBP were modeled with logistic and multivariable regression adjusted for age, sex, body mass index, cardiovascular risk factors, lifestyle/habitual factors, apnea–hypopnea index, and race/ethnicity. In the overall cohort, prevalent hypertension was modestly associated with PLMS index (10 U; odds ratio, 1.05; 95% confidence interval, 1.00–1.10) and PLMS arousal index (1 U; 1.05; 1.01–1.09) after adjusting for confounders. Association in the overall cohort was influenced by large effect sizes in blacks, in whom the odds of prevalent hypertension increased by 21% (1%–45%) for 10-U PLMS index increase and 20% (2%–42%) for 1-U PLMS arousal index increase. In blacks, every 1-U PLMS arousal index increase was associated with SBP 1.01 mm Hg higher (1.01; 0.04–1.98). Associations between PLMS and blood pressure outcomes were also suggested among Chinese-Americans but not in whites or Hispanics. In a multiethnic cohort of community-dwelling men and women, prevalent hypertension and SBP are associated with PLMS frequency in blacks.
Insomnia With Physiological Hyperarousal Is Associated With Hypertension

Abstract

Previous studies have suggested that insomnia with objective short sleep duration is associated with a higher risk of hypertension, and it has been speculated that the underlying mechanism is physiological hyperarousal. In this study, we tested whether insomnia with physiological hyperarousal measured by Multiple Sleep Latency Test (MSLT), a standard test of sleepiness/alertness, is associated with increased risk of hypertension. Two hundred nineteen chronic insomniacs and 96 normal sleepers were included in this study. Chronic insomnia was defined based on standard diagnostic criteria with symptoms lasting ≥6 months. All subjects underwent 1 night in laboratory polysomnography followed by a standard MSLT. We used the median mean MSLT value (ie, >14 minutes) and the 75th percentile of mean MSLT value (ie, >17 minutes) to define hyperarousal. Hypertension was defined based either on blood pressure measures or on diagnosis treatment by a physician. After controlling for age, sex, body mass index, apnea–hypopnea index, diabetes mellitus, smoking, alcohol, and caffeine use, insomnia combined with MSLT >14 minutes increased the odds of hypertension by 300% (odds ratio=3.27; 95% confidence interval=1.20–8.96), whereas insomnia combined with MSLT >17 minutes increased even further the odds of hypertension by 400% (odds ratio=4.33; 95% confidence interval=1.48–12.68) compared with normal sleepers with MSLT ≤14 minutes. Insomnia associated with physiological hyperarousal is associated with a significant risk of hypertension. Long MSLT values may be a reliable index of the physiological hyperarousal and biological severity of chronic insomnia.

Pathological Effects of Obstructive Apneas During the Sleep Cycle in an Animal Model of Cerebral Small Vessel Disease

Abstract

We tested the hypothesis that apneas during the sleep cycle exacerbate hypertension and accelerate changes that occur with cerebral small vessel disease. Obstructive sleep apnea was modeled by intermittent inflations of a chronically implanted tracheal balloon to occlude the airway during the sleep cycle (termed OSA) in spontaneously hypertensive stroke–prone (SHRSP) rats, a model of cerebral small vessel disease. SHRSP rats and their parent strain, Wistar Kyoto (WKY) rats, were exposed to OSA for 2 weeks (from 9 to 11 or from 18 to 20 weeks). At 9 weeks, hypertension was developing in the SHRSP rats and was firmly established by 18 weeks. OSA exposure increased systolic blood pressure in SHRSP rats by ≈30 mm Hg in both age groups compared with shams that were surgically prepared but not exposed to OSA (P<0.05). OSA exposure also increased systolic blood pressure in WKY rats by 20 and 37 mm Hg at 11 and 20 weeks, respectively (P<0.05). OSA exposure in SHRSP rats compromised blood–brain barrier integrity in white matter at both 11 and 20 weeks of age when compared with SHRSP sham rats (P<0.05). Microglia were activated in SHRSP rats exposed to OSA but not in sham rats at 11 weeks (P<0.05). At 20 weeks, microglia were activated in sham SHRSP rats (P<0.05) compared with WKY sham rats and were not further activated by OSA. Neither was blood–brain barrier integrity altered nor microglia activated in any of the WKY groups. We conclude that OSA accelerates the onset of the cerebral pathologies associated with cerebral small vessel disease in SHRSP, but not WKY, rats.

Effects of Continuous Positive Airway Pressure Treatment on Clinic and Ambulatory Blood Pressures in Patients With Obstructive Sleep Apnea and Resistant Hypertension: A Randomized Controlled Trial

Abstract

The effect of continuous positive airway pressure (CPAP) on blood pressures (BPs) in patients with resistant hypertension and obstructive sleep apnea is not established. We aimed to evaluate it in a randomized controlled clinical trial, with blinded assessment of outcomes. Four hundred thirty-four resistant hypertensive patients were screened, and 117 patients with moderate/severe obstructive sleep apnea, defined by an apnea–hypopnea index ≥15 per hour, were randomized to 6-month CPAP treatment (57 patients) or no therapy (60 patients), while maintaining antihypertensive treatment. Clinic and 24-hour ambulatory BPs were obtained before and after 6-month treatment. Primary outcomes were changes in clinic and ambulatory BPs and in nocturnal BP fall patterns. Intention-to-treat and per-protocol (limited to those with uncontrolled ambulatory BPs) analyses were performed. Patients had mean (SD) 24-hour BP of 129(16)/75(12) mm Hg, and 59% had uncontrolled ambulatory BPs. Mean apnea–hypopnea index was 41 per hour and 58.5% had severe obstructive sleep apnea. On intention-to-treat analysis, there was no significant difference in any BP change, neither in nocturnal BP fall, between CPAP and control groups. The best effect of CPAP was on nighttime systolic blood pressure in per-protocol analysis, with greater reduction of 4.7 mm Hg (95% confidence interval, −11.3 to +3.1 mm Hg; P=0.24) and an increase in nocturnal BP fall of 2.2% (95% confidence interval, −1.6% to +5.8%; P=0.25) in comparison with control group. In conclusion, CPAP treatment had no significant effect on clinic and ambulatory BPs in patients with resistant hypertension and moderate/severe obstructive sleep apnea, although a beneficial effect on nighttime systolic blood pressure and on nocturnal BP fall might exist in patients with uncontrolled ambulatory BP levels.
Patent Foramen Ovale Closure in Obstructive Sleep Apnea Improves Blood Pressure and Cardiovascular Function

Abstract
Obstructive sleep apnea (OSA) is a frequent syndrome characterized by intermittent hypoxemia and increased prevalence of arterial hypertension and cardiovascular morbidity. In OSA, the presence of patent foramen ovale (PFO) is associated with increased number of apneas and more severe oxygen desaturation. We hypothesized that PFO closure improves sleep-disordered breathing and, in turn, has favorable effects on vascular function and arterial blood pressure. In 40 consecutive patients with newly diagnosed OSA, we searched for PFO. After initial cardiovascular assessment, the 14 patients with PFO underwent initial device closure and the 26 without PFO served as control group. Conventional treatment for OSA was postponed for 3 months in both groups, and polysomnographic and cardiovascular examinations were repeated at the end of the follow-up period. PFO closure significantly improved the apnea–hypopnea index (DeltaAHI =−7.9±10.4 versus +4.7±13.1 events/h; P=0.009; PFO closure versus control) and the oxygen desaturation index (DeltaODI =−7.6±16.6 versus +7.6±17.0 events/h; P=0.01), and the number of patients with severe OSA decreased significantly after PFO closure (79% versus 21%; P=0.007). The following cardiovascular parameters improved significantly in the PFO closure group, although remained unchanged in controls: brachial artery flow–mediated vasodilation, carotid artery stiffness, nocturnal systolic and diastolic blood pressure (−7 mm Hg, P=0.009 and −3 mm Hg; P=0.04, respectively), blood pressure dipping, and left ventricular diastolic function. In conclusion, PFO closure in OSA patients improves sleep-disordered breathing and nocturnal oxygenation. This translates into an improvement of endothelial function and vascular stiffening, a decrease of nighttime blood pressure, restoration of the dipping pattern, and improvement of left ventricular diastolic function.

Genetic and Functional Evidence Supports LPAR1 as a Susceptibility Gene for Hypertension

Abstract
Essential hypertension is a complex disease affected by genetic and environmental factors and serves as a major risk factor for cardiovascular diseases. Serum lysophosphatidic acid correlates with an elevated blood pressure in rats, and lysophosphatidic acid interacts with 6 subtypes of receptors. In this study, we assessed genetic association of lysophosphatidic acid receptors with essential hypertension by genotyping 28 single-nucleotide polymorphisms from genes encoding for lysophosphatidic acid receptors, LPAR1, LPAR2, LPAR3, LPAR4, LPAR5, and LPAR6 and their flanking sequences, in 3 Han Chinese cohorts consisting of 2630 patients and 3171 controls in total. We identified a single-nucleotide polymorphism, rs531003 in the 3′-flanking genomic region of LPAR1, associated with hypertension (the Bonferroni corrected  \( P=1.09×10^{−5} \), odds ratio [95% confidence interval]=[1.23 [1.13–1.33]). The risk allele C of rs531003 is associated with increased expression of LPAR1 and the susceptibility of hypertension, particularly in those with a shorter preterm ( \( P=4.73×10^{−5} \), odds ratio [95% confidence interval]=1.75 [1.34–2.28]). We further demonstrated that blood pressure elevation caused by sleep deprivation and phenylephrine-induced vasoconstriction was both diminished in LPAR1-deficient mice. Together, we show that LPAR1 is a novel susceptibility gene for human essential hypertension and that stress, such as shortage of sleep, increases the susceptibility of patients with risk allele to essential hypertension.

Chronic Intermittent Hypoxia and Hypercapnia Inhibit the Hypothalamic Paraventricular Nucleus Neurotransmission to Parasympathetic Cardiac Neurons in the Brain Stem

Abstract
Obstructive sleep apnea is associated with chronic intermittent hypoxia/hypercapnia (CIHH) episodes during sleep that heighten sympathetic and diminish parasympathetic activity to the heart. Although one population of neurons in the paraventricular nucleus of the hypothalamus strongly influences sympathetic tone and has increased activity after CIHH, little is known about the role of this pathway to parasympathetic neurons and how this network is altered in CIHH. We hypothesized that CIHH inhibits the excitatory pathway from the paraventricular nucleus of the hypothalamus to parasympathetic cardiac vagal neurons in the brain stem. To test this hypothesis, channelrhodopsin was selectively expressed, using viral vectors, in neurons in the paraventricular nucleus of the hypothalamus, and channelrhodopsin-expressing fibers were photoactivated to evoke postsynaptic currents in cardiac vagal neurons in brain stem slices. Excitatory postsynaptic currents were diminished in animals exposed to CIHH. The paired-pulse and prolonged facilitation of the postsynaptic current amplitudes and frequencies evoked by paired and bursts of photoactivation of channelrhodopsin fibers, respectively, occurred in unexposed rats but were blunted in CIHH animals. In response to an acute challenge of hypoxia/hypercapnia, the amplitude of postsynaptic events was unchanged during, but increased after hypoxia/hypercapnia in unexposed animals. In contrast, postsynaptic currents were inhibited during hypoxia/hypercapnia in rats exposed to CIHH. In conclusion, the excitatory pathway to cardiac vagal neurons is diminished in response to both acute and chronic exposures to hypoxia/hypercapnia. This could elicit a reduced cardioprotective parasympathetic activity and an enhanced risk of adverse cardiovascular events in episodes of apnea and chronic obstructive sleep apnea.
Simvastatin Treatment Attenuates Increased Respiratory Variability and Apnea/Hypopnea Index in Rats With Chronic Heart Failure

Abstract
Cheyne-Stokes respiration and cardiac arrhythmias are associated with increased morbidity and mortality in patients with chronic heart failure (CHF). Enhanced carotid body chemoreflex (CBC) sensitivity is associated with these abnormalities in CHF. Reduced carotid body (CB) nitric oxide and nitric oxide synthase (NOS) levels play an important role in the enhanced CBC. In other disease models, simvastatin (statin) treatment increases endothelial NOS, in part, by increasing Kruppel-like factor 2 expression. We hypothesized that statin treatment would ameliorate enhanced CBC sensitivity, as well as increased respiratory variability, apnea/hypopnea index, and arrhythmia index, in a rodent model of CHF. Resting breathing pattern, cardiac rhythm, and the ventilatory and CB chemoreceptor afferent responses to hypoxia were assessed in rats with CHF induced by coronary ligation. CHF was associated with enhanced ventilatory and CB afferent responses to hypoxia, as well as increased respiratory variability, apnea/hypopnea index, and arrhythmia index. Statin treatment prevented the increases in CBC sensitivity and the concomitant increases in respiratory variability, apnea/hypopnea index, and arrhythmia index. Kruppel-like factor 2 and endothelial NOS protein were decreased in the CB and nucleus tractus solitarii of CHF animals, and statin treatment increased the expression of these proteins. Our findings demonstrate that the increased CBC sensitivity, respiratory instability, and cardiac arrhythmias observed in CHF are ameliorated by statin treatment and suggest that statins may be an effective treatment for Cheyne-Stokes respiration and arrhythmias in patient populations with high chemoreflex sensitivity.

Obstructive Sleep Apnea and Hypertension: An Update

Extract
Obstructive sleep apnea is highly relevant to patients with hypertension. These 2 conditions frequently coexist (an estimated 50% of patients with hypertension have concomitant obstructive sleep apnea), and recent evidence supports the notion that obstructive sleep apnea represents the most prevalent secondary contributor to elevated blood pressure in patients with resistant hypertension.

Key Points
Epidemiological evidence implicates obstructive sleep apnea as one of the modifiable and highly prevalent factors in the development of hypertension. A nocturnal non-dipping pattern of BP has been confirmed in older adults with obstructive sleep apnea but not in children.

Patients with obstructive sleep apnea have decreased exercise tolerance and higher diastolic blood pressure during exercise testing.

Conflicting data exist regarding the role of continuous positive airway pressure in reducing incident hypertension in patients with obstructive sleep apnea.

Results of meta-analyses speak consistently to a modest 2-mm Hg antihypertensive effect of continuous positive airway pressure.

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Disclosures
None.

References


