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Effect of Nasal Continuous Positive Airway Pressure Treatment on Blood Pressure in Patients With Obstructive Sleep Apnea

Heinrich F. Becker, MD; Andreas Jerrentrup, MD; Thomas Ploch, Dipl Psych; Ludger Grote, MD; Thomas Penzel, PhD; Colin E. Sullivan, MD; J. Hermann Peter, MD

Background—There is increasing evidence that obstructive sleep apnea (OSA) is an independent risk factor for arterial hypertension. Because there are no controlled studies showing a substantial effect of nasal continuous positive airway pressure (nCPAP) therapy on hypertension in OSA, the impact of treatment on cardiovascular sequelae has been questioned altogether. Therefore, we studied the effect of nCPAP on arterial hypertension in patients with OSA.

Methods and Results—Sixty consecutive patients with moderate to severe OSA were randomly assigned to either effective or subtherapeutic nCPAP for 9 weeks on average. Nocturnal polysomnography and continuous noninvasive blood pressure recording for 19 hours was performed before and with treatment. Thirty two patients, 16 in each group, completed the study. Apneas and hypopneas were reduced by ≈95% and 50% in the therapeutic and subtherapeutic groups, respectively. Mean arterial blood pressure decreased by 9.9±11.4 mm Hg with effective nCPAP treatment, whereas no relevant change occurred with subtherapeutic nCPAP (P=0.01). Mean, diastolic, and systolic blood pressures all decreased significantly by ≈10 mm Hg, both at night and during the day.

Conclusions—Effective nCPAP treatment in patients with moderate to severe OSA leads to a substantial reduction in both day and night arterial blood pressure. The fact that a 50% reduction in the apnea-hypopnea index did not result in a decrease in blood pressure emphasizes the importance of highly effective treatment. The drop in mean blood pressure by 10 mm Hg would be predicted to reduce coronary heart disease event risk by 37% and stroke risk by 56%. (***Circulation.*** **2003;107:68-73.)**

Key Words: hypertension ■ cardiovascular diseases ■ sleep ■ blood pressure

In recent years it has been shown that obstructive sleep apnea (OSA) is a common disorder in adults.[1] OSA is characterized by repetitive apneas and hypoxia caused by upper airway collapse during sleep, despite respiratory efforts of the diaphragm. Five or more apneas per hour of sleep are generally considered abnormal, and severely affected patients have several hundred apneas each night. Most apneas and hypopneas are terminated by a transient arousal from sleep and consecutive hyperventilation. Disruption of normal sleep by frequent arousals leads to excessive daytime sleepiness, the most prominent symptom in these patients.

Nocturnal arterial blood pressure is increased in OSA patients, and there is increasing evidence that OSA is an independent risk factor for arterial hypertension during the day.[2–5] Although the exact mechanisms are still unclear, a persistent increase in sympathetic tone caused by chronically occurring repetitive hypoxia and arousal are thought to be the key mechanisms for the short- and long-term blood pressure increases in OSA.[6,7] It has also recently been shown that patients with OSA have an impairment of resistance-vessel endothelium-dependent vasodilation.[8]

Nasal continuous positive airway pressure (nCPAP) has become the standard treatment for OSA[9] and has been shown in controlled studies to reduce symptoms and improve quality of life in OSA patients.[10,11] Controlled studies showed either no effect[12,13] or only a minor decrease in arterial blood pressure by 1.4 and 2.5 mm Hg, respectively.[14,15] The effectiveness of this treatment on cardiovascular sequelae in OSA patients has been questioned altogether.[16] Therefore, we performed a prospective randomized trial to evaluate the effect of nCPAP on arterial blood pressure in OSA patients.

Methods

Patients and Protocol

The study was conducted in the Sleep Unit at the University Hospital in Marburg, Germany. The Unit takes adult patients referred by general practitioners (≈35%), pneumologists (≈35%), or other subspecialties (≈30%). During the study period, 283 patients ful-

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From the Department of Respiratory Medicine, Philipps-University Marburg, Marburg, Germany, and the Department of Medicine, David Read Laboratory, University of Sydney, Australia (C.E.S.).
Dr Sullivan is a minor shareholder of ResMed Inc.
Correspondence to Heinrich F. Becker, Innere Med, Pneumologie, Baldingerstr D-35033 Marburg, Germany. E-mail HF.Becker@mailer.uni-marburg.de

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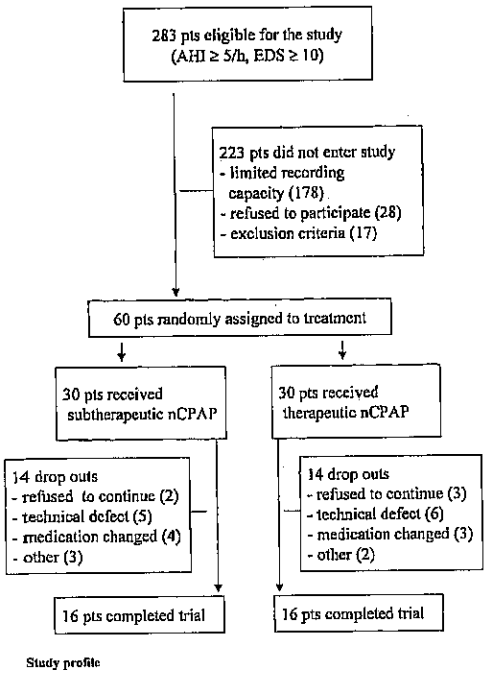

Figure 1. Study profile. EDS indicates excessive daytime sleepiness.

filled the inclusion criteria of ≥5 apneas or hypopneas per hour of sleep and excessive daytime sleepiness (10 or more points out of a maximum of 24 on the Epworth sleepiness scale[17]; Figure 1). A maximum of 4 patients per week could be included in the study. If there was more than one patient eligible on one day, the patient with the most pronounced sleep apnea according to an ambulatory recording was asked first to participate in the study.

Exclusion criteria were predominantly central sleep apnea, respiratory failure, heart failure (NYHA class III or IV), myocardial infarction 3 months before the study, and relevant cardiac arrhythmia (second- and third-degree heart block or premature ventricular contractions in Lown classes IV or V). Professional drivers were also excluded. The local ethics committee approved the study, and all subjects gave written informed consent.

Sixty consecutive patients who consented to participate underwent baseline diagnostic polysomnography and continuous noninvasive blood pressure recording for 19.1±1.3 hours using the Portapres device (TNO Biomedical Instrumentation).

Patients were then randomized to receive either effective or subtherapeutic nCPAP treatment. Randomization was performed on the telephone by a person who was otherwise not involved in the study.

All study patients spent another 2 nights in the sleep laboratory to ensure adaptation to the nasal mask. Treatment was done with either the Sullivan IV (ResMed) or the Aria (Respironics) nCPAP device. In the effective treatment group, treatment pressure was increased until apneas, hypopneas, and snoring were prevented during all sleep stages and with the patient lying supine. Effective treatment pressure was 9.1±2.3 cm H_2O on average (range, 6 to 12 cm H_2O). In the subtherapeutic treatment group, pressure was left unchanged at the lowest possible value for the nCPAP device used (3 or 4 cm H_2O, respectively).

Patients then went home on the prescribed treatment for an average of 65.2±49.6 days. They were then readmitted to the sleep laboratory, and polysomnography and continuous blood pressure measurements during daytime and sleep were repeated on either subtherapeutic or effective nCPAP treatment. Compliance was objectively measured by the built-in compliance software of the nCPAP devices.

TABLE 1. Anthropometric Data and Relevant Diagnoses

	Therapeutic nCPAP	Subtherapeutic nCPAP	*P*
Age, y	54.4±8.9	52.3±8.4	NS
Sex, male:female	15:1	14:2	NS
Body mass index, kg/m²	33.3±5.1	33.5±6.0	NS
Epworth sleepiness scale	14.4±2.5	14.1±3.2	NS
Arterial hypertension, n	8/16	13/16	NS

Any antihypertensive medication the patients were taking at the beginning of the study remained unchanged throughout the entire study. Patients were considered dropouts if antihypertensive medication was accidentally changed by the patient or their general practitioner.

In 28 patients the study could not be completed because of technical problems with the blood pressure device (n=11), a change in antihypertensive treatment (n=7, 3 in the effective and 4 in the subtherapeutic nCPAP group), or the patient did not want to continue the study (n=8) or did not tolerate treatment (n=2).

Complete measurements were available in 32 patients, 16 on effective and 16 on subtherapeutic nCPAP. These data are reported here. Although arterial hypertension was neither an inclusion nor an exclusion criterion, 8 of 16 patients in the effective group and 13 of 16 patients in the subtherapeutic group turned out to be hypertensive (15 of these patients were on antihypertensive treatment and 6 had an office blood pressure of 160 and/or 90 mm Hg or more). Seven of the 15 patients on antihypertensive medication were treated with one drug (ACE inhibitor, n=4; angiotensin II receptor blocker, n=2; and calcium channel blocker, n=1). A combination of 2 antihypertensive drugs was used in 7 patients (angiotensin II receptor blocker plus diuretic, n=4; ACE inhibitor plus diuretic, n=1; ACE inhibitor plus β-blocker, n=1; and calcium channel blocker plus diuretic, n=1), and one patient was on a combination of 4 antihypertensives (ACE inhibitor, diuretic, calcium channel blocker, and α-blocker).

Anthropometric data and relevant diagnoses are shown in Table 1.

Measurements

Sleep Study Recordings

Polysomnography was performed and visually scored according to standard criteria,[18,19] as detailed previously.[20] The average number of apneas and hypopneas per hour of sleep (apnea-hypopnea index [AHI]) was calculated.

Blood Pressure Recording

The Portapres is a battery-operated portable instrument to measure arterial blood pressure continuously and noninvasively with 2 finger cuffs.[21,22] Portapres provides a height correction to compensate for hydrostatic level effects due to movements of the measured finger with respect to the reference point at heart level. Blood pressure values measured by Portapres are in good concordance with invasively measured values[21,23,24] and are highly reproducible.[24,25] Because of the battery we were using, recording time was limited to ≈20 hours. After the elimination of artifacts, an average of 19.1±1.3 hours of blood pressure recordings were analyzed. During the diagnostic sleep study, patients spent 7.2±1 hours in bed and 7.1±1 hours on treatment. Nighttime blood pressure was calculated for this time period. Daytime blood pressure was thus recorded during the remaining 12 hours.

Patients were allowed to move freely in the hospital, but they were not able to climb stairs because the equipment was mounted on an infusion pole.

After the recording, blood pressure data were processed automatically with the software of the device, including the built-in artifact removal. No further processing of the data was done by the investigators. For each minute of the recording, the software of the device calculated mean, systolic, and diastolic blood pressure as well as heart rate.

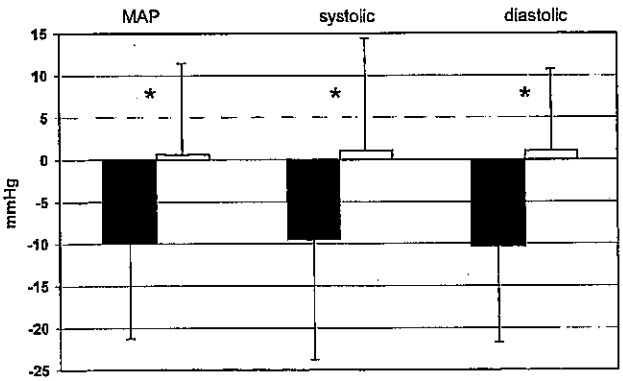

Figure 2. Changes in blood pressure with effective (closed bars) and subtherapeutic (open bars) nCPAP. *Significant difference. MAP indicates mean arterial blood pressure; systolic, systolic blood pressure; and diastolic, diastolic blood pressure. MAP, $P=0.01$; systolic blood pressure, $P=0.04$; diastolic blood pressure, $P<0.005$.

Statistics

Mean arterial blood pressure during the entire recording period was the primary outcome variable. Secondary outcome variables were systolic and diastolic blood pressure during the entire recording period, as well as daytime and nighttime mean, systolic, and diastolic blood pressures. Tertiary outcome variables were the changes in polysomnographic parameters (AHI, sleep stages, SaO_2) and sleepiness (Epworth sleepiness scale).

Statistical analysis was performed using the SPSS statistical package, version 10.0 (SPSS). Two-factor ANOVA (group versus time) with repeated measures on the factor time (baseline minus treatment) was used to test the effect of therapeutic versus subtherapeutic nCPAP. To test for differences between the 2 treatment groups at baseline and for differences in nCPAP compliance, the unpaired t test (2 sided) was used. Data are reported as mean±SD unless otherwise stated. Statistical significance was assumed at $P\leq0.05$.

Results

There was a decrease in mean arterial blood pressure over the 19.1±1.3-hour recording period by 9.9±11.4 mm Hg in the therapeutic nCPAP group, but an increase by 0.6±10.8 mm Hg in the subtherapeutic nCPAP group ($P=0.01$, ANOVA interaction time by group). Both diastolic and systolic blood pressures also decreased significantly by 10.3±11.4 mm Hg and 9.5±15.0 mm Hg, respectively, with therapeutic nCPAP ($P<0.005$ and $P=0.04$, respectively, ANOVA interaction time by group) compared with subtherapeutic nCPAP (Figure 2). The decrease in mean blood pressure with effective nCPAP was present both during the day (−10.0±12.1 mm Hg) and night (−10.3±15.3 mm Hg). These effects of subtherapeutic and therapeutic nCPAP on blood pressure are summarized in Table 2. The time course of mean arterial blood pressure before and on treatment for both groups is shown in Figure 3. In the effective treatment group, mean arterial blood pressure decreased during the entire recording period; the most pronounced drop occurred during the night and in the morning until about noon. In the afternoon and evening, the blood pressure decrease was still

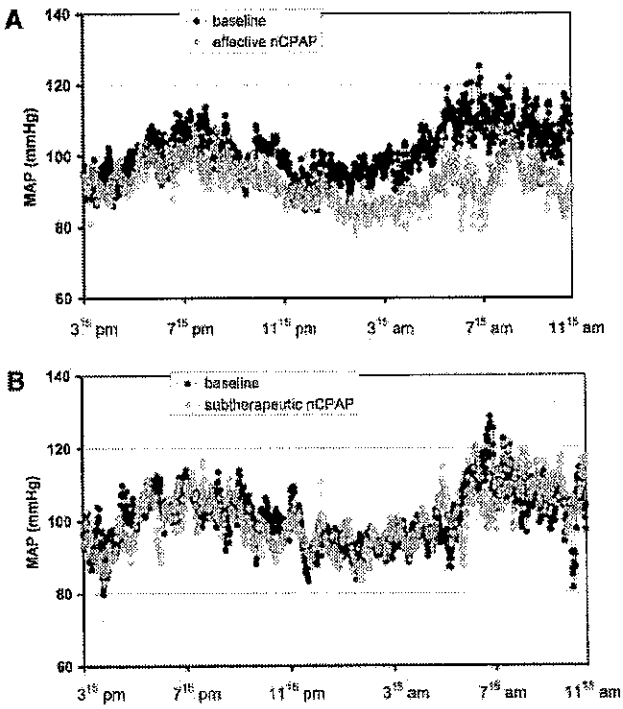

Figure 3. A, Time course of mean arterial blood pressure (MAP) before (closed circles) and on treatment (open circles) with therapeutic nCPAP. On average, 7.2±1 hours were recorded during the night. B, Time course of mean arterial blood pressure (MAP) before (closed circles) and on treatment (open circles) with subtherapeutic nCPAP. On average, 7.1±1 hours were recorded during the night.

TABLE 2. Blood Pressure (mm Hg) at Baseline and on Treatment

	Baseline			Treatment		Difference in Blood Pressure Changes (95% CI)	P (ANOVA, Interaction Time by Group)
	Therapeutic nCPAP	Subtherapeutic nCPAP	P	Therapeutic nCPAP	Subtherapeutic nCPAP		
Mean blood pressure	100.4±15.9	99.5±12.3	NS	90.6±10.4	100.1±9.5	−10.5 (−18.5 to −2.4)	0.01
Systolic	135.9±17.5	136.2±13.1	NS	126.4±14.3	137.3±11.1	−10.6 (−20.8 to −0.3)	0.04
Diastolic	83.4±15.9	81.1±12.3	NS	73.1±10.5	82.1±9.1	−11.3 (−19.0 to −3.7)	0.005
Mean daytime blood pressure	103.6±16.1	103.5±12.1	NS	93.6±11.3	104.8±10.6	−11.3 (−19.7 to −2.7)	0.01
Systolic	140.1±17.6	141.0±13.8	NS	132.1±15.7	143.2±11.2	−10.3 (−20.6 to 0.1)	0.05
Diastolic	86.4±16.1	85.4±12.3	NS	75.8±11.6	85.9±10.6	−11.2 (−19.5 to −2.8)	0.01
Mean nighttime blood pressure	96.2±17.6	93.6±15.2	NS	85.9±10.9	94.7±9.6	−11.4 (−21.4 to −1.3)	0.03
Systolic	129.9±20.0	129.2±16.9	NS	118.5±13.9	130.4±12.6	−12.6 (−25.5 to 0.2)	0.05
Diastolic	79.1±17.0	75.4±15.2	NS	69.6±10.1	77.3±7.9	−11.4 (−20.7 to −2.1)	0.02

TABLE 3. Polysomnography at Baseline and on Treatment

	Baseline			Treatment		
	Therapeutic nCPAP Group	Subtherapeutic nCPAP Group	*P*	Therapeutic nCPAP Group	Subtherapeutic nCPAP Group	*P* (ANOVA, Interaction Time by Group)
Epworth sleepiness scale*	14.4±2.5	14.1±3.2	NS	5.1±3.8	8.9±5.0	0.009
AHI, n/h	62.5±17.8	65.0±26.7	NS	3.4±3.1	33.4±29.2	0.001
TST, min	349.4±42.7	341.8±59.3	NS	375.6±44.5	351.2±66.9	NS
NREM I/II, % of TST	82.4±11.6	79.7±11.2	NS	62.5±8.0	67.3±12.3	NS
NREM III/IV, % of TST	6.2±7.2	6.0±8.4	NS	15.2±7.1	11.6±6.7	NS
REM, % of TST	11.4±6.8	14.3±6.3	NS	22.3±5.7	21.1±8.8	NS
Arousal, n/h	58.7±21.9	62.0±28.0	NS	24.1±9.8	41.2±27.2	NS
Mean SaO_2, %	89.9±4.0	90.2±4.9	NS	95.5±1.7	92.5±4.0	0.04
Minimum SaO_2, %	64.1±14.7	61.2±14.9	NS	80.5±16.8	72.0±15.7	NS
SaO_2 <90%, % of TST	33.6±28.8	36.2±26.5	NS	1.1±2.5	19.8±25.7	NS

TST indicates total sleep time; REM, rapid eye movement sleep; NREM I/II, nonrapid eye movement sleep stages I and II; and NREM III/IV, nonrapid eye movement sleep stages III and IV.

*Maximum score: 24.

present, but less pronounced, when compared with the night and the first part of the day.

The results of polysomnography before and on treatment are presented in Table 3. There were no significant differences in any of the variables between the 2 groups at baseline. Except for total sleep time, all parameters improved with both treatment modalities. The improvements of AHI, sleepiness, and mean SaO_2 were significantly larger with therapeutic nCPAP compared with subtherapeutic nCPAP (ANOVA interaction time by group).

Compliance with nCPAP was high in both groups: the average use per night was 5.5±2.0 hours in the therapeutic and 5.4±2.2 hours in the subtherapeutic group (*P*=NS). Body weight was similar in both groups at baseline (103.1± 16.5 kg and 102.6±17.8 kg in the therapeutic and subtherapeutic groups, respectively; *P*=NS), and it remained virtually unchanged (103.0±16.0 kg and 102.3±17.1 kg in the therapeutic and subtherapeutic groups, respectively; *P*=NS, ANOVA interaction time by group).

Discussion

After an average of 65 days of treatment, we found a decrease in mean arterial blood pressure by 9.9 mm Hg with effective nCPAP, whereas there was a slight increase in blood pressure with subtherapeutic nCPAP. Mean, diastolic, and systolic blood pressures decreased significantly during both the day and night by between 8.1 and 11.4 mm Hg. Although subtherapeutic nCPAP led to a significant reduction of AHI by ≈50%, blood pressure did not decrease.

There is general agreement that nCPAP treatment leads to a reversal of apnea-associated short-term blood pressure increases during sleep[26,27]; however, the effect on daytime blood pressure is uncertain. Whereas 3 uncontrolled studies found a 24-hour blood pressure decrease with nCPAP,[25,27,28] 4 controlled studies found no significant decrease[12,13] or only a minor blood pressure reduction (1.4 and 2.5 mm Hg, respectively).[14,15]

In contrast to these previously published controlled studies, our data show a pronounced reduction in day and night blood pressure with therapeutic nCPAP. Several factors may explain the discrepancy in the results. (1) The different results may have been caused by the fact that treatment duration was substantially longer in our study and that the use of nCPAP was high in our patients. (2) A total of 21 of our 32 patients were hypertensive, because mainly patients with moderate to severe OSA were included, whereas hypertensives were excluded in one study[14] or less prevalent in the others.[12,13] (3) The different methods of blood pressure measurement will influence the results. It has been shown that 24-hour ambulatory blood pressure measurement causes arousal from sleep in 64% of the recordings and leads to an increase in systolic and diastolic blood pressure by 13.7±15.9 mm Hg and 3.7±8.2 mm Hg, respectively.[29] The ambulatory blood pressure measurement will therefore underestimate the changes in nighttime blood pressure caused by nCPAP. An important advantage of Portapres is that it does not cause arousal from sleep.[30] Furthermore, continuous blood pressure data, as measured in our study, are in good concordance with invasively measured blood pressures, are highly reproducible,[21] and therefore more accurately mirror the actual blood pressure than intermittent measurements.

There was no relevant change in body weight in either group, so this factor did not contribute to our results.

The increase in sympathetic activity caused by apnea-associated repetitive asphyxia and arousal are thought to be the key mechanisms in the pathogenesis of daytime arterial hypertension in patients with OSA. Treatment with nCPAP attenuates the increase in sympathetic activity.[31] In an animal model, repetitive obstructive apneas and acoustic arousal from sleep led to a similar increase in nighttime blood pressure. However, recurrent arousal from sleep without airway obstruction did not lead to an increase in daytime blood pressure, whereas sustained hypertension developed if apneas had been produced in the animals.[32] Although most

polysomnographic parameters improved more markedly with effective compared with subtherapeutic nCPAP, apart from the AHI and Epworth sleepiness scale scores, only mean SaO_2 was significantly higher on therapeutic than on subtherapeutic nCPAP. This finding further emphasizes the role of hypoxia in the evolution of daytime arterial hypertension and the importance of preventing hypoxia to achieve optimal treatment of arterial hypertension in OSA patients.

In our study there was a substantial number of drop outs, mainly because of technical problems and changes in antihypertensive medication. Portapres is a complex device and is therefore more prone to technical problems than ambulatory blood pressure measurement. Because technical defects and accidental changes in medication occurred in both groups in a similar number of patients, this should not have influenced our results.

The reduced number of patients that could be included in the final analysis has reduced power from the statistical tests performed; however, because of the large effect of therapeutic nCPAP on blood pressure, differences in primary and secondary outcome variables were significant.

We used a single-blind study design because a method for applying therapeutic and subtherapeutic nCPAP in a double-blind fashion was not available. The knowledge of the allocation to one or the other treatment group might have influenced the analysis of our data. Polysomnography was therefore scored by a technician who was not informed about the study, and blood pressure analysis, including artifact recognition and elimination, was done exclusively by the software of the Portapres device. The risk of a bias due to the single-blind design was thus minimized.

Unexpectedly, nCPAP at a pressure of 3 or 4 cm H_2O reduced mean AHI by ≈50%, improved sleep structure, and reduced desaturation. NCPAP at the pressure applied is therefore not a placebo but a suboptimal form of treatment, because even the low treatment pressure used here may be sufficient to at least partly reverse upper airway obstruction in many patients. However, the reduction in AHI in the control group would have acted against our hypothesis that nCPAP lowers blood pressure. Despite the reduction in AHI in the subtherapeutic treatment group by ≈50%, there was no reduction in blood pressure in this group. The unexpected result that suboptimal nCPAP has a substantial effect on AHI but no effect on blood pressure emphasizes the importance of optimal treatment to reduce cardiovascular sequelae.

This is the first prospective, randomized study to demonstrate a substantial reduction in arterial blood pressure during both the day and night with ≈9 weeks of therapeutic nCPAP treatment compared with subtherapeutic nCPAP. Although AHI was reduced by 50% with subtherapeutic nCPAP, there was no effect on blood pressure, emphasizing the importance of optimal treatment. In our study, the drop in mean blood pressure was close to 10 mm Hg. This would be predicted to reduce coronary heart disease event risk by 37% and stroke risk by 56%.[33]

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