Long-term effects of nocturnal continuous positive airway pressure therapy in patients with resistant hypertension and obstructive sleep apnea

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Abstract

Obstructive sleep apnea (OSA) is often linked to high blood pressure and has a particularly high prevalence in patients with resistant hypertension. The effect of continuous positive airway pressure (CPAP) therapy on blood pressure (BP) values has been evaluated in several short-term clinical trials with conflicting results. Our aim was to investigate the role of long-term CPAP treatment in achieving BP control in patients who associate OSA and resistant hypertension. We have included in the study 33 patients with resistant hypertension, diagnosed with OSA in our sleep lab. Data was collected initially and after a mean follow-up period of 4 years. Patients were divided into 2 groups according to the use of CPAP therapy. Patients under CPAP therapy (n=12) exhibited a higher reduction in both systolic and diastolic pressure and BP control was achieved in 75% of cases, while patients without CPAP treatment (n=21) remained with refractory hypertension in proportion of 90.5%. A de-escalation of antihypertensive drug regimen by discontinuation of 1 or more drugs was observed in 41.6% (n=5) of patients from CPAP group and in the other 33.4% (n=4) the medication remained unchanged, but BP control was reached. Using a direct logistic regression model for examining the impact of different confounders on the probability of diagnosis of resistant hypertension at follow-up, the only statistically significant predictor found was the lack of CPAP usage.
Keywords: *sleep apnea, resistant hypertension, CPAP therapy, blood pressure control*

Rezumat

Efectele pe termen lung ale terapiei cu presiune continuă pozitivă nocturnă la pacienții cu hipertensiune rezistentă și sindrom de apnee de somn

Sindromul de apnee de somn obstructivă (OSA) este corelat cu hipertensiune arterială și are o prevalență crescută în grupul pacienților cu hipertensiune rezistentă. Efectele terapiei cu presiune pozitivă continuă (CPAP) asupra tensiunii arteriale (BP) au fost evaluate în câteva studii clinice, iar rezultatele obținute rămân contradictorii. Scopul nostru a fost de a investiga rolul CPAP pe termen lung în obținerea controlului asupra BP la pacienții care asociază OSA și hipertensiune rezistentă. Am inclus în studiu 33 de pacienți cu hipertensiune arterială rezistentă, diagnosticați anterior cu OSA în laboratorul nostru. Colectarea datelor s-a făcut la includerea în studiu și după o perioadă medie de urmărire de 4 ani. Pacienții au fost împărțiți în grupe în funcție de utilizarea terapiei CPAP. Lotul celor care au fost tratați cu CPAP (n=12) a înregistrat o mai bună reducere a tensiunii sistolice, cât și diastolice, iar controlul BP s-a obținut în 75% din cazuri. Pe de altă parte, în grupul celor fără CPAP (n=21) persistența hipertensiunii refractare s-a înregistrat în 90,5% din cazuri. O reducere a tratamentului antihipertensiv s-a remarcat în grupul tratat cu CPAP: întreruperea a minimum un medicament antihipertensiv în 41,6% din cazuri (n=5). În restul de 33,4% (n=4) medicația a rămas nemodificată, dar s-a observat controlul BP. Prin folosirea unui model de regresie logistică pentru examinarea impactului factorilor de confuzie, cât și a probabilității diagnostice a hipertensiunii rezistente, singura observație cu semnificație statistică demonstrată a fost lipsa tratamentului cu CPAP.
Cuvinte-cheie: *sindrom de apnee de somn, hipertensiune rezistentă, tratament cu CPAP, control tensiune arterială*

There is a developing body of information establishing the connection between sleep disordered breathing (SDB) and high blood pressure. Both conditions are highly prevalent and carry a significant risk for cardiovascular morbidity and mortality[1,2].

The correlation between severity of sleep apnea (OSA) and the presence of hypertension was shown in a number of large epidemiological surveys[3,5]. Although the two conditions share similar risk factors, like obesity and older age[6,7], there are also data suggesting that SDB is an independent risk factor for hypertension[3,8], the presence of OSA being a predictor for the occurrence of hypertension[3] or poor blood pressure (BP) control[5].

Another important observation is the connection between sleep apnea and resistant hypertension - defined as blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive drugs of different classes[7]. The prevalence of OSA in patients with resistant hypertension varies between 56% and 85%, according to different authors[6,9-12], while for the prevalence of resistant hypertension among patients with OSA there is trivial or no information in the literature.

A pathophysiological link between OSA and resistant hypertension could be the increased aldosterone excretion. Calhoun et al. have found evidence of increased

aldosterone excretion in subjects with resistant hypertension and symptoms of sleep apnea[13]. While the causality of this association is unknown, it was hypothesized that sleep apnea contributes to the development of resistant hypertension by stimulating aldosterone excretion. On the other hand, increased levels of aldosterone seen in patients with resistant hypertension seem to correlate with severity of OSA[12].

Several studies have assessed the effect of CPAP therapy on BP values. Campos-Rodriguez et al. found that long-term CPAP reduces BP modestly, with significant reductions in BP only in those patients with higher BP at entry and good CPAP compliance[14]. In a meta-analysis of placebo-controlled randomized trials, Haentjens et al. reached similar conclusions[15]. Other authors have demonstrated the beneficial effect of CPAP therapy in reducing BP in patients with OSA and resistant hypertension during a single night of CPAP use and after 3 months of treatment[16, 17]. Nevertheless, most were small studies with short follow-up periods. An older long-term observational study found a beneficial response to CPAP therapy, but primarily in subjects with the most severe hypertensive disease[18]. Given the fact that a drop in mean blood pressure by 10 mmHg would be predicted to reduce coronary heart disease event risk by 37% and stroke risk by 56%, more research is needed into the effect of CPAP therapy on BP, especially in patients who associate OSA and resistant hypertension[19,20].

Aim

The aim of the study was to analyze the long-term effects of CPAP therapy on BP values in patients with OSA and resistant hypertension.

Methods

This was a retrospective case-control study. The Ethical Committee of "Victor Babeș" University of Medicine and Pharmacy Timișoara approved the study protocol.

Patients were recruited from those referred to the Sleep Laboratory of "Victor Babeș" Infectious Diseases and Pulmonology Hospital Timișoara with a clinical suspicion of sleep apnea and a diagnosis of hypertension. Informed consent was obtained from all patients before they were involved in the study[21]. The initial visit to our lab was reviewed for baseline data.

We included in the analysis patients who fulfilled the following criteria: polygraphic/ polysomnographic confirmation of the diagnosis of OSA, ability to complete a sleep questionnaire and a measured and documented medical history of resistant hypertension, defined as a persistent elevated daytime blood pressure (>140 mmHg systolic or > 90 mmHg diastolic) despite the concomitant use of 3 antihypertensive agents of different classes in a stable dose[7].

The exclusion criteria were: absence of data from the notes, inability to collect clinical information through sleep questionnaires both at the initial and at follow-up visits, missing or incomplete initial sleep studies, a diagnosis of central sleep apnea, coexistent lung cancer or pregnancy, documented noncompliance with antihypertensive drugs and the presence of an identifiable secondary cause of hypertension (other than OSA) that would explain resistance to treatment.

We retrieved and analyzed all the medical records of the patients who had a sleep study in our lab from 2001 to 2011.

Patients identified with a diagnosis of hypertension were invited for an additional clinical review between 2012-2014, in order to assess the effect of CPAP therapy on their BP values. The patients identified as non compliant with CPAP treatment served as our control group. Patients under CPAP therapy were considered compliant if they had followed the treatment at least 6 consecutive months prior to follow-up evaluation.

At the study visit all patients had their medical and drug history reviewed, had a clinical examination, completed a sleep questionnaire and an additional sleep study.

The use of antihypertensive medication was determined on the basis of participants' answers to questions concerning the current use of alpha-I-adrenergic blockers, beta-blockers, calcium-channel blockers, diuretics, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, direct vasodilators, alpha-II-agonists and other centrally acting drugs for the treatment of hypertension.

In addition, the initial and the highest historical BP reading was noted, as well as the disease duration, antihypertensive drug regimen used and the presence of other cardiovascular comorbidities such as coronary artery disease, arrhythmias, heart failure and stroke. Other concomitant diseases and medications were also recorded.

Additional office blood pressure measurements were performed at the study visit with the same standard blood pressure manual machine (standard mercury sphygmomanometer FAZZINI, Italy).

Demographic data and anthropometric measurements were systematically collected: age, sex, weight (in kilograms), height (in centimeters), neck, waist and hip circumference (in centimeters), waist-hip ratio and skinfold thickness (in centimeters) of the suprailiac area.

The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. Each patient's data were recorded on a standardized template sheet.

Sleepiness was assessed by the administration of Epworth questionnaire with eight questions, four response options and a score range between 0 and 24. A score of 10 or more was considered significant for excessive daytime sleepiness.

After administration of the questionnaires and after participants had been seated for at least 15 minutes, one or two readings of systolic and diastolic blood pressure were obtained at 5-minute intervals with the use of conventional mercury sphygmomanometry.

Apnea-hypopnea index was assessed through cardiorespiratory polygraphy or complete polysomnography.

The devices used for polygraphy were POLY-MESAM 4 (1998) and STARDUST RESPIRONICS (2005). Both allowed the collection of air flow (oral or nasal), oxygen saturation, pulse rate, body position, body movements, ambient light, snoring, thoracic respiratory effort, nasal CPAP pressure and air flow. Each automatic recording was then reviewed and manually validated by qualified sleep lab personnel.

A 32-35 channel polysomnographic recording system (model ALICE 5 RESPIRONICS 2005) was used to assess the sleep state and respiratory and cardiac variables. The sleep technicians affixed the leads on each patient and then performed calibration. Sleep state was measured with electroencephalography, electrooculography, and chin electromyography. These signals were used to determine the sleep stage for each 30-second interval of the polysomnographic record, according to conventional criteria[22].

Arterial oxyhemoglobin saturation, oral and nasal airflow, nasal air pressure and rib-cage and abdominal respiratory motion were used to assess episodes of sleep-disordered breathing. Oxyhemoglobin saturation was continuously recorded with a pulse oximeter. Nasal cannula detected nasal airflow. Piezoelectric transducers recorded rib-cage and abdominal excursions. Sleep stage and respiratory events were assessed by trained sleep technicians. Each 30-second interval of the polysomnographic record was inspected visually for episodes of abnormal breathing. Cessation of airflow for at least 10 seconds was defined as an episode of apnea. A discernible reduction in the sum amplitude of the rib-cage plus the abdominal excursions on respiratory inductance plethysmography that lasted at least 10 seconds and that was associated with a reduction in the oxyhemoglobin saturation of at least 4 percent was defined as an episode of hypopnea. The apnea-hypopnea index (AHI) was defined as the average number of episodes of apnea and hypopnea per hour of objectively measured sleep and was the summary measurement of the occurrence of sleep-disordered breathing.

Statistical analysis

Data was stored electronically using Microsoft Excel 2007 and processed using IBM-SPSS, version 18, 2010. The threshold value of statistical significance was set at $p<0.05$. Mathematical values of comparisons tests were declared significant, according to the statistical program output. If the tests were not significant ($p\geq0.05$) only p value was reported. The probability (p value) was declared at each applied test with up to three decimal places. Mean, median and standard deviations expressed to two decimal places were used as presentation for tabulation of scale type data, whereas group percentage with one decimal place was used as presentation for tabulation of ordinal data. For comparisons of parametric data, we used the t test. For nonparametric or ordinal data, we used the Mann-Whitney test (comparing two groups). The chi-square test was used in 2x2 Tables with ordinal/ nominal data. Mixed analysis of variance of the general linear model of repeated measures was used to show the interaction between group and time of variables measured at 2 points: baseline and follow-up. We used a logistic regression model to measure the relationship between resistant hypertension and OSA.

Results

From the total number of 1329 patients screened, we identified 168 patients with a clinical suspicion of sleep apnea and a diagnosis of resistant hypertension.

Among the 168 patients identified with resistant hypertension, 132 met the inclusion criteria. Of these, 74 had missing contact details or could not be reached, 23 patients declined participation in the study and 2 patients died. Follow-up study data has been collected from the remaining 33 patients. From the group included in the analysis we identified 12 patients (36.4%) who were compliant with CPAP therapy and 21 (63.6%) who were non compliant.

The mean follow-up period was 50.95 ± 15.59 months for patients in non-CPAP group and 46.41 ±21.11 months for patients in the CPAP group.

The severity of OSA expressed by AHI was found to differ significantly between the groups at baseline ($p=0.015$) (Table I). Yet, according to AHI, all patients enrolled in this study, except one from non-CPAP group, had severe forms of OSA.

No statistically significant differences were found at baseline between CPAP and non-CPAP group regarding age, gender, BMI, anthropometric measurements (neck, abdominal and waist circumference), mean follow-up period and the presence of excessive daytime sleepiness (ESS) evaluated by Epworth scale.

Smoking was found at baseline in nine (42.9%) of the patients from non-CPAP group, four patients (19%) were ex-smokers and eight patients (38.1%) never smoked, while in the CPAP group, no patient was an active smoker at baseline, three patients (25%) were ex-smokers and 9 patients (75%) never smoked. At follow-up no change of smoking status was noticed in the CPAP group, while in non-CPAP group, two patients stopped smoking.

No statistically significant difference between the two groups was found at the initial visit regarding mean duration of hypertension (expressed in years) and mean values of maximum systolic and diastolic pressure and actual systolic and diastolic pressure (Table II).

The prevalence of resistant hypertension was significantly lower at follow-up in patients from the CPAP group, compared with patients from non-CPAP group ($\chi^2(1)=14.73$, $p=0,001$) - Figure 1.

The odds of having resistant hypertension after a mean follow-up period of 50.95 months was 28.5 (95% confidence interval: 4.02 - 201.74) for the patients from non-CPAP group. The attributable fraction (AF) in lowering the odds of resistant hypertension for the CPAP treatment was 72.7%, with an absolute risk reduction (ARR) of 65.5% and a number needed to treat (NNT) of 1.5.

We used a direct logistic regression model in order

Table 1 Patient's characteristics at baseline

	CPAP (n=12)	Non-CPAP (n=12)	p Value
Age, years	55.58 ± 5.99	54.14 ± 8.29	0.602
Sex (men/women), no.	7/5	11/10	0.741
BMI, kg/m²	38.17 ± 8.88	36.38 ± 5.56	0.538
Neck circumference, cm	45.92 ± 4.88	44.81 ± 3.75	0.471
Abdominal circumference, cm	125.92 ± 17.91	121.62 ± 9.79	0.455
Waist circumference, cm	126.92 ± 19.97	119.57 ± 9.57	0.251
Mean follow-up period, m	46.41 ± 21.11	50.95 ± 15.59	0.485
ESS, score	11.67 ± 4.84	12.62 ± 4.57	0.548
AHI, no. of events/h	65.83 ± 23.31	47.13 ± 17.90	0.015

Table 2 Hypertension history at baseline

	CPAP (n=12)	Non-CPAP (n=12)	p Value
Mean duration of HTA, years	9.67 ± 4.84	11.57 ± 9.69	0.459
Mean maximum systolic pressure, mm Hg	207.50 ± 28.00	195.71 ± 26.56	0.238
Mean maximum diastolic pressure, mm Hg	122.08 ± 13.72	122.14 ± 22.05	0.993
Mean actual systolic pressure, mm Hg	147.92 ± 19.70	152.86 ± 17.92	0.468
Mean actual diastolic pressure, mm Hg	95.83 ± 13.79	95.71 ± 16.30	0.983

to evaluate the impact of different variables on the probability of having resistant hypertension. The following confounders have not been found to contribute significantly to this model: initial systolic and diastolic pressure, maximum systolic and diastolic pressure, smoking and alcohol consumption. The model using 2 predictors: CPAP use (Y/N) and BMI value was statistically significant (χ^2=19.7, p<0.001). The strongest predictor for the presence of resistant hypertension at follow-up was the lack of CPAP use (OR=67.3). BMI value did not contribute significantly to the model, but the result was very close to statistical significance (p=0.065).

At follow-up, in the CPAP group we have found a decrease in both mean systolic and diastolic pressure, but statistical significance was obtained only for diastolic values (p=0.003). Mean systolic and diastolic pressure decreased as well in non-CPAP group at follow-up and statistical significance was seen only in diastolic pressure (p=0.011). However, a trend was observed, with a higher decrease in mean systolic and diastolic values in the CPAP group, but without statistical significance (Wilks' lambda=0.91, p=0.50 and Wilks' lambda=0.98, p=0.45, respectively) –Figure 2a, 2b.

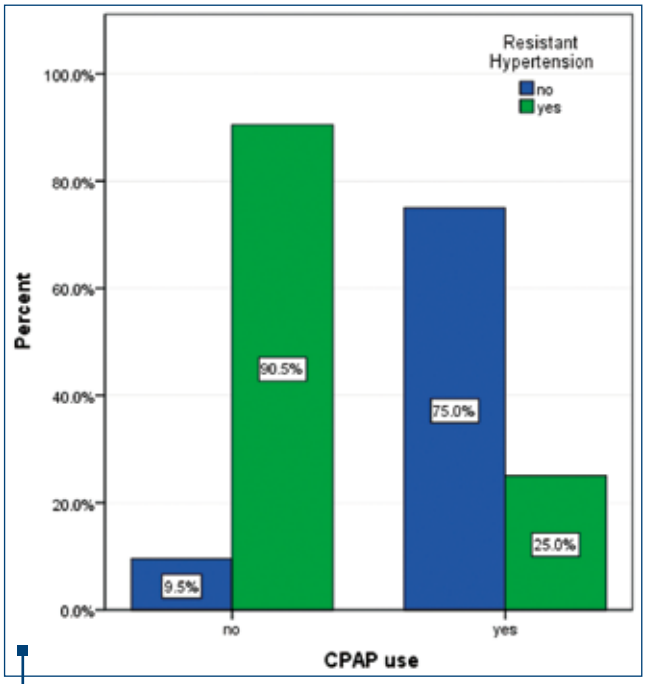

Figure 1. *Prevalence of resistant hypertension at follow-up in CPAP and non-CPAP group*

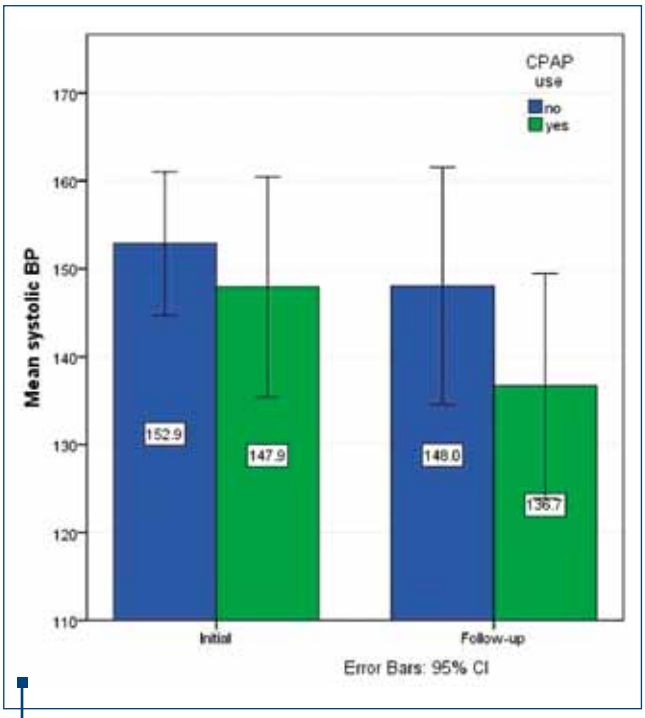

Figure 2a. *Mean systolic pressure evolution in CPAP and non-CPAP group*

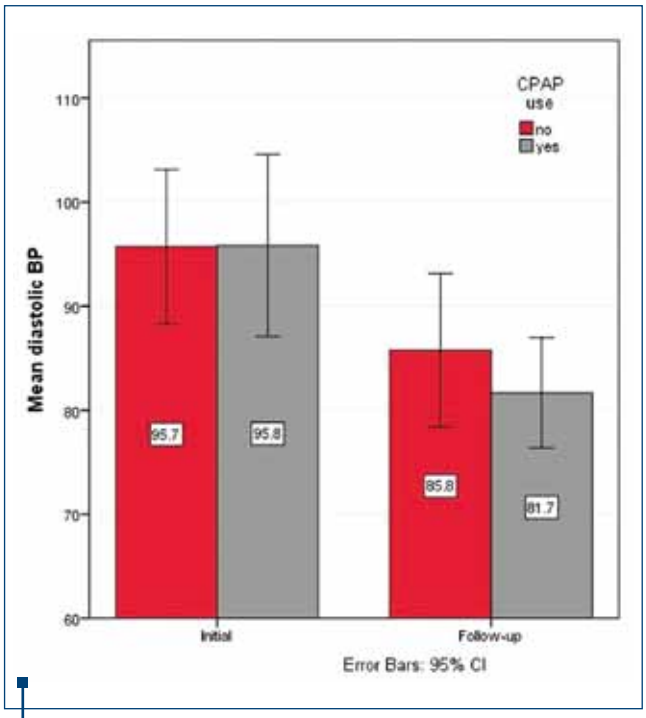

Figure 2b. *Mean diastolic pressure evolution in CPAP and non-CPAP group*

Conclusion and discussion

This retrospective study suggests that long-term CPAP treatment in patients with OSA and resistant hypertension may have a significant contribution to the achievement of blood pressure control.

These results are particularly important for the management of those patients with refractory forms of hypertension secondary to the presence of OSA. Due to the negative impact of sleep-disordered breathing on cardiovascular disease, by treating OSA and at the same time reaching blood pressure control, CPAP therapy may have a strong benefit in lowering cardiovascular morbidity and mortality. The symptoms of OSA may also improve by controlling BP, as some recent data suggest[23].

These results are consistent with already published data. Many authors have attempted to appraise the effect of CPAP therapy on BP values with discordant results[14, 15, 24, 25]. Nevertheless, it has been clearly shown that CPAP treatment may have a beneficial effect in lowering BP values in patients with severe forms of hypertension, e.g. resistant hypertension[16, 18] and a good compliance with CPAP therapy (> 4 hours at night on CPAP)[26]. Several prospective trials have likewise confirmed the positive result of CPAP therapy in lowering BP in patients with refractory hypertension, but all these studies are lacking the evidence of longer-term health outcomes of CPAP therapy[17, 27].

The present paper analyzed specifically the role of long-term CPAP therapy in achieving BP control in patients who associate sleep apnea and resistant hypertension. After a mean period of 4 years, patients under CPAP therapy exhibited a higher decrease in both systolic and diastolic pressure and BP control was achieved in 75% of cases, while patients without CPAP treatment remained with refractory hypertension in proportion of 90.5%. A de-escalation of antihypertensive drug regimen by discontinuation of 1 or more drugs was seen in 41.6% (n=5) of patients from CPAP group and in the other 33.4% (n=4) the medication remained unchanged, but BP control was reached.

Failure to demonstrate a statistically significant decrease of BP values in patients from CPAP group compared with patients from non-CPAP group is primarily explained by the relatively small number of patients and probably by the lack of 24-hour blood pressure monitoring[17]. The decrease in BP values seen in patients from non-CPAP group might be explained in our opinion by the fact that 28.5% (n=6) of these patients had an escalation of their antihypertensive medication by adding of 1 or more drugs. Another factor could be the increasing awareness of the hypertensive disease and its consequences.

Our study differs from other retrospective analysis because we had as control group patients with untreated OSA. However, our study has also a number of specific limitations. First, BP values were assessed only by office measurements. Secondly, even if we identified a potentially larger patient population, we only managed to collect data from a relatively small number of patients. Nevertheless, the number of patients in our analysis was comparable with similar studies. Thirdly, an accurate compliance of CPAP therapy could not be recorded, due to the fact that only a few CPAP machines were fitted with data storage medium.

There is a number of confounding factors that can

influence both OSA and BP control. Existing data indicate that among these variables, measures of habits seem to be the stronger confounders, rather than smoking and alcohol use[3]. Obesity is highly prevalent both in hypertensive and sleep apnea patients and may be a strong confounder. In our study, there was no statistically significant difference in BMI between CPAP and non-CPAP group at baseline (p=0.538) and at follow-up (p=0.636). Using a direct logistic regression model for analyzing the impact of different confounders on the probability of having resistant hypertension, the only statistically significant predictor was found to be the lack of CPAP usage.

In summary, we conclude that diagnosing and treating OSA in patients with resistant hypertension may represent a valuable intervention for achieving blood pressure control. Knowing that a reduction of mean arterial BP by 5% to 10% in hypertensive patients has the potential to reduce stroke incidence by at least 40%[28, 29], CPAP therapy of associated sleep apnea may have a substantial contribution to the reduction of negative cardiovascular and cerebrovascular consequences of uncontrolled hypertension. Further, large, prospective, randomized trials are required to clarify the validity of our observations. ■

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