CHEST

Original Research

SLEEP DISORDERS

Effects of OSA Treatment on BP in Patients With Resistant Hypertension

A Randomized Trial

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Background: **OSA is extremely common among patients with resistant hypertension (HTN). However, the impact of the treatment of OSA with CPAP on BP in patients with resistant HTN is not well established.**

Methods: **In the current study, 40 patients with confirmed resistant HTN and moderate to severe OSA confirmed by full polysomnography were randomized to medical therapy or to medical treatment plus CPAP for 6 months. Patients were evaluated at study baseline and after 6 months by 24-h ambulatory BP monitoring (ABPM).**

Results: **Thirty-five patients (77% men; age, 56 ± 1 years; BMI, median 32 kg/m² [25%-75%, 28-39 kg/m²]; apnea-hypopnea index, 29 events/h [24-48 events/h]; Epworth Sleepiness Scale, 10 ± 1; systolic/diastolic office BP, 162 ± 4/97 ± 2 mm Hg; taking four [four to five] antihypertensive drugs) completed the study. CPAP was used for 6:01 ± 0:20 h/night (3:42-7:44 h/night). Compared with the control group, awake systolic/diastolic ABPM decreased significantly in the CPAP group (Δ: +3.1 ± 3.3 /+2.1 ± 2.7 mm Hg vs −6.5 ± 3.3/−4.5 ± 1.9 mm Hg, respectively, $P < .05$). Interestingly, the BP changes were observed only while patients were awake, but not during nocturnal ABPM (Δ: +2.8 ± 4.5/+1.8 ± 3.5 mm Hg vs +1.6 ± 3.5/+0.8 ± 2.9 mm Hg, P = NS).**

Conclusions: **The treatment of OSA with CPAP significantly reduces daytime BP in patients with resistant HTN. Therefore, our study reinforces the importance of recognizing and treating OSA in patients with resistant HTN.**

Trial registry: **ClinicalTrials.gov; No.: NCT00812695; URL: www.clinicaltrials.gov**

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Abbreviations: ABPM = ambulatory BP monitoring; HTN = hypertension

It is estimated that one-third of the hypertensive population has resistant hypertension (HTN), defined as uncontrolled BP despite the concurrent use of three antihypertensive agents, including a diuretic, or the need for more than three medications to control BP.[1] Egan et al[2] found that the prevalence of resistant HTN has been increasing over the past decades. However, despite the increasing prevalence of resistant HTN, many patients do not take their medications correctly and cannot be classified as having resistant HTN.[1] Patients with true resistant HTN are at increased risk of target organ damage and cardiovascular complications compared with patients with well-controlled HTN.[3] Therefore, continuous efforts to improve BP control among patients with true resistant HTN are mandatory.

Among the potential strategies for controlling BP, active recognition and treatment of the secondary causes of HTN may have a beneficial impact on the management of patients with resistant HTN. OSA is a common condition characterized by repetitive episodes of upper airway obstruction during sleep. The

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biologic mechanisms by which OSA is potentially deleterious to the cardiovascular system include intermittent hypoxia, intrathoracic pressure changes generating mechanical stress on the heart and large arteries, and frequent arousals from sleep. All these components may trigger increased sympathetic activity, systemic

inflammation, oxidative stress, and endothelial dysfunction, which ultimately may contribute to increased BP.[4]

CPAP is the standard treatment for moderate to severe OSA. Regular use of CPAP during sleep can reduce BP in hypertensive patients.[5] OSA is, therefore, a recognized secondary cause of HTN.[1] OSA is also independently associated with a higher frequency of target organ damage.[6] Indeed, the presence of OSA and HTN in the same individual appears to have an additive effect on the occurrence of vascular injury and cardiac remodeling, compared with each factor individually.[7] We have shown that OSA is by far the most common condition associated with resistant HTN.[8] However, the impact of OSA treatment on BP control among patients with true resistant HTN is poorly understood. To date, only three nonrandomized trials[5,9,10] and a post hoc analysis of a subgroup of patients with resistant HTN[11] have explored the impact of OSA treatment on BP, pointing to a sustained BP reduction. Therefore, we hypothesized that CPAP would significantly decrease BP in patients with resistant HTN.

Materials and Methods

Subjects

Patients with resistant HTN from the Hypertension Unit, Heart Institute (InCor), University of São Paulo Medical School, with no previous diagnosis of OSA, were invited to undergo overnight polysomnography, and those with moderate to severe OSA (apnea-hypopnea index $\geq$ 15 events/h) were selected. All participants were evaluated for 2 months before randomization, with pill count every 2 weeks. We considered adherent patients to be those taking all medications correctly $>$ 80% of the time on all days, as described previously.[12] This run-in period was important to carefully exclude pseudoresistance due to poor medication adherence and white coat HTN. Subjects who were older than 65 years or younger than 30 years, as well as those with other secondary causes of HTN as described previously (arrhythmias, heart failure, valvular heart disease, renal failure, smoking, regular alcohol intake, or taking any medication that increases BP), were excluded from the study. The local Ethics Committee approved the protocol (approval No. 0745/07), and all participants gave written informed consent. No patients were included in the protocol before study registration.

Blood Samples

Venous blood was collected from all the participants for the measurement of glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, and RBC count. Plasmatic aldosterone concentration was determined in the early morning (7:00-9:00 AM) by using standard techniques. All blood was collected before and after study termination.

Office BP

BP measurements were determined by the average results of two readings of systolic and diastolic BP obtained at 5-min intervals using a mercury sphygmomanometer, after participants had been seated in a chair, with feet on the floor and arm supported at heart level, for at least 5 min.[13]

24-h Ambulatory BP Monitoring

24-h ambulatory BP monitoring (ABPM) was evaluated using a Spacelabs Healthcare device (model 90207), as described previously.[14] Patients were classified as having normal awake BP if the corresponding value was $<$ 135 mm Hg systolic and $<$ 85 mm Hg diastolic.[15] Normal sleep BP was considered to be $<$ 120/70 mm Hg.[15] Overall 24-h normality was defined as $<$ 130/80 mm Hg. Nondipping was defined as a BP decrease of $<$ 10% during sleep compared with the awake period. Bedtime and the time of awakening from sleep were recorded in diaries. Therefore, data are based on 24-h ABPM using actual sleep and wake times recorded by participants.

Sleep Evaluation

All patients underwent overnight polysomnography (Embla - Flaga hf. Medical Devices), as described previously.[16] Apneas were defined as a total absence of oronasal flow for $\geq$ 10 s and hypopneas as a clear decrease ($>$ 50%) in amplitude of oronasal flow for $\geq$ 10 s, followed by a 3% desaturation and/or arousal. The apnea-hypopnea index was obtained by dividing the total number of apneas and hypopneas by total sleep time. In addition, subjective daytime sleepiness was evaluated by using the Epworth Sleepiness Scale.[17] Patients randomized to CPAP underwent a full-night CPAP titration study, during which the pressure was adjusted to abolish apnea and hypopnea, as described previously.[18]

Study Design

Patients were randomly assigned to standard HTN treatment (control) or HTN treatment plus OSA treatment with CPAP for 6 months. An independent staff created blocked randomization lists, balancing the population according to sex and OSA severity. Patients were evaluated for pill count once a week in the first month and once a month thereafter. In accordance with the study protocol, prescriptions were not changed during the study. CPAP compliance was objectively measured monthly by downloading a card that contained the time counter of the device. Office and 24-h ABPM was performed at study entry and after 6 months. At the end of the study, CPAP was offered and initiated in the patients randomized to the control arm.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SEM or median (interquartile range) when appropriate. Qualitative variables are

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expressed as percentages. A two-tailed unpaired Student *t* test for independent samples or a χ^2 test was used to compare baseline variables in the two groups. The percentage of patients who presented a normal pattern of nocturnal BP dipping before and after treatment was evaluated using the McNemar test. Repeated-measures two-factor analysis of variance (group vs time) was used to test the effect of CPAP on BP and aldosterone levels in the intervention group vs no CPAP in the control group before and after 6 months. A value of $P < .05$ was considered significant. Sample size was calculated to assess a minimum reduction of 5 ± 5 mm Hg in systolic BP after CPAP treatment, assuming an α error of 5% and a statistical power of 80%. The resulting sample size was 16 patients per treatment group (CPAP and control). We estimated 25% of study losses, resulting in a sample size of 40 patients. All patients randomized to CPAP were analyzed using an intention-to-treat principle regardless of their compliance with the treatment. Drug compliance was monitored carefully. We excluded patients with poor compliance because this would have been an important confounder. Data were analyzed with SPSS 17.0 statistical software (IBM).

Results

We initially recruited 243 patients with clinical suspicion of resistant HTN; 179 (74%) presented OSA and 203 were excluded, resulting in a sample of 40 patients (Fig 1) with moderate to severe OSA and resistant HTN, who were randomized to the CPAP or the control group. No patients presented central sleep apnea (all participants presented central apneas of <5 events/h of sleep). Before entering this study, none of the patients had received a prior diagnosis of OSA. During the study, five patients were excluded because of poor drug compliance (n = 4) or acute myocarditis (n = 1). Therefore, our final sample comprised 35 patients (Fig 1), who were predominantly middle-age obese men (Table 1[19]). Except for BMI and waist circumference, the patients assigned to the control or CPAP group were similar regarding all main parameters, including age, glucose, lipid profile, office BP, heart rate, and sleep variables (Tables 1, 2).

The optimal CPAP pressure determined in the patients assigned to CPAP during the titration sleep study was 11.5 ± 0.5 cm H_2O (range, 7.0-5.0 cm H_2O). CPAP decreased the apnea-hypopnea index to 5 events/h (range, 4-9 events/h) and raised the minimum oxygen saturation to 88% (range, 85%-91%). The CPAP was used on average for 6:01 ± 0:20 h per night (range, 3:42-7:44 h per night), and none of the patients discontinued CPAP during the study. Only one patient (5%) used CPAP for <4 h/night. Compared with the control group, there was a trend for improvement in daytime somnolence in the CPAP group after follow-up (Epworth Δ: $+1.0 \pm 1.2$ vs -2.9 ± 1.6; $P = .06$) and no significant changes in BMI (Δ BMI: +0.4 kg/m^2

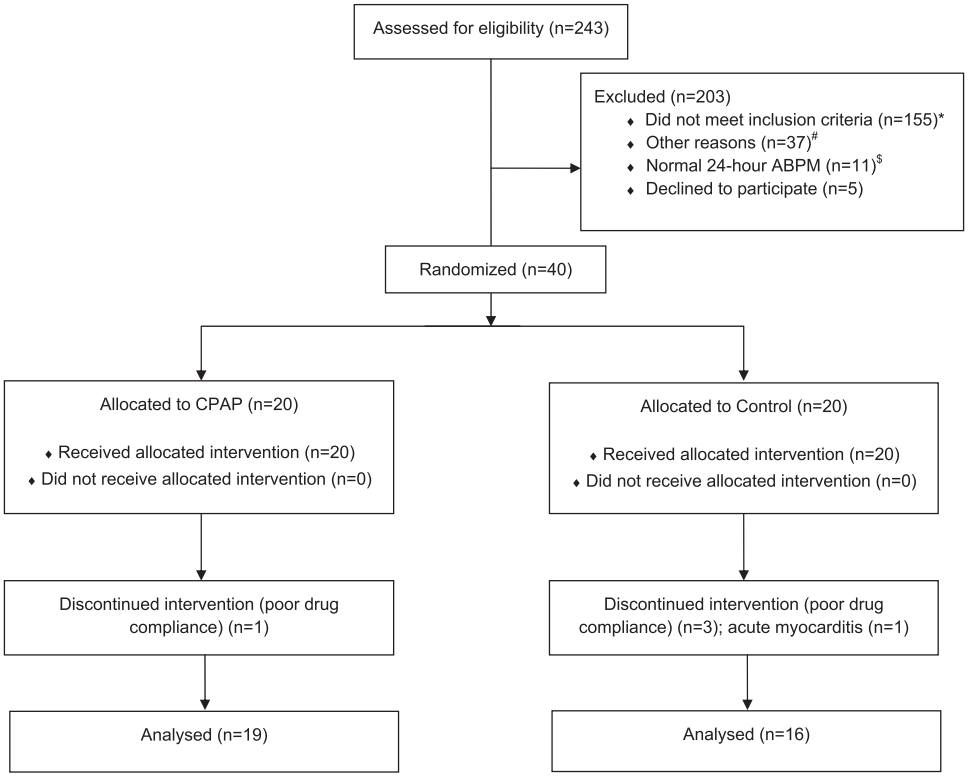

Figure 1. Patient flowchart. *Did not present moderate to severe OSA (n = 64), had normalized BP after run-in period (n = 48), presented chronic renal failure or other secondary cause of hypertension (n = 21), aged >65 years (n = 22). #Not localized/difficult access to hospital. $Controlled BP with more than three drugs (n = 11). ABPM = ambulatory BP monitoring.

Table 1—*Baseline Anthropometrics and Clinical Characteristics*

Anthropometrics and Clinical Characteristics	Total (N = 35)	Control (n = 16)	CPAP (n = 19)	*P* Value
Age, y	56 ± 1	55 ± 2	57 ± 2	.36
Male	77	81	74	.45
BMI, kg/m²	32 (28-39)	29 (27-33)	36 (31-41)	.01
Neck circumference, cm	42 ± 1	40 ± 1	43 ± 1	.09
Waist circumference, cm	107 ± 2	100 ± 3	113 ± 3	.01
White	57	44	68	.11
Diabetes mellitus	60	56	63	.74
Dyslipidemia	86	88	84	.78
Metabolic syndrome[a]	83	75	90	.38
Familial history of HTN	89	88	90	1.00
Heart rate, bpm	66 ± 2	66 ± 4	66 ± 3	.97
Systolic BP, mm Hg	162 ± 4	161 ± 7	163 ± 4	.78
Diastolic BP, mm Hg	97 ± 2	96 ± 3	97 ± 3	.70
Drugs, No.	6 (5-8)	6 (4-7)	8 (6-9)	.08
Antihypertensive drugs, No.	4 (4-5)	4 (3-5)	4 (4-5)	.12
Thiazides/loop diuretics	100	100	100	1.00
β-Blocker	83	81	84	.58
ACEI	63	56	68	.50
Calcium channel blocker	77	81	74	.45
ARB	31	31	32	1.00
Central sympatholytic (clonidine/methyldopa)	43	25	58	.09

Data are presented as mean ± SEM or %, or, for variables with skewed distribution, median (interquartile range). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; bpm = beats per min; HTN = hypertension.
[a]Based on National Cholesterol Education Program, Adult Treatment Panel III.[19]

[−0.2 to 1.1] kg/m² vs +0.5 kg/m² [−0.4 to 1.1] kg/m², $P = .88$).

No patients changed antihypertensive medication or presented any clinically relevant event related to HTN during the study period. The daytime systolic and diastolic ABPM at study entry and termination were 145.8 ± 4.0/88.4 ± 3.4 and 148.8 ± 3.8/90.6 ± 2.7 mm Hg vs 148.4 ± 2.5/85.4 ± 2.3 and 141.9 ± 3.3/80.9 ± 2.7 mm Hg in the control and CPAP groups, respectively. The nocturnal systolic and diastolic ABPM at study entry and termination were 136.6 ± 4.4/78.4 ± 3.4 and 139.3 ± 3.4/80.3 ± 2.7 mm Hg vs 136.2 ± 3.0/75.4 ± 2.8 and 137.8 ± 3.5/76.2 ± 2.7 mm Hg in the control and CPAP groups, respectively. Compared with the control group, awake systolic/diastolic ABPM decreased significantly in the CPAP group (Δ: +3.1 ± 3.3/+2.1 ± 2.7 mm Hg vs −6.5 ± 3.3/−4.5 ± 1.9 mm Hg, respectively, $P < .05$). The percentage of

Table 2—*Baseline Laboratory and Sleep Study Characteristics*

Variable	Total (N = 35)	Control (n = 16)	CPAP (n = 19)	*P* Value
Laboratory variables				
Creatinine, mg/dL	1.2 (0.9-1.4)	1.2(0.9-1.3)	1.2 (0.9-1.5)	.22
Fasting glucose, mg/dL	112 (103-151)	111 (104-137)	123 (103-167)	.51
Cholesterol, mg/dL	196 (147-230)	214 (171-229)	193 (128-234)	.42
LDL cholesterol, mg/dL	109 ± 6	110 ± 8	107 ± 9	.85
HDL cholesterol, mg/dL	40 (31-52)	39 (34-51)	41 (28-52)	.64
Triglycerides, mg/dL	164 (122-225)	185 (130-234)	151 (103-211)	.25
Hemoglobin, g/dL	14.4 ± 0.2	14.9 ± 0.3	14.0 ± 0.3	.07
Aldosterone, ng/dL	10.6 ± 1.1	9.4 ± 1.3	11.7 ± 1.6	.28
Sleep variables				
Epworth Sleepiness Scale, score	10 ± 1	9 ± 1	12 ± 1	.11
AHI, events/h	29 (24-48)	28 (22-38)	36 (24-51)	.42
Arousals, No./h	22 (14-32)	21 (15-33)	26 (14-32)	.78
Awake Sao_2, %	95 (93-96)	95 (94-97)	95 (93-96)	.30
Mean Sao_2, %	93 (91-94)	93 (92-96)	93 (89-94)	.38
Lowest Sao_2, %	81 (75-85)	84 (78-86)	81 (73-83)	.09
Desaturation index, No./h	21 (13-43)	17 (15-34)	22 (12-47)	.56
$Sao_2 < 90\%$, % of sleep time	2.9 (0.7-17.3)	1.8 (0.5-8.7)	5.4 (1.7-48)	.06

Data are presented as mean ± SEM or, for variables with skewed distribution, median (interquartile range).
AHI = apnea-hypopnea index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Sao_2 = arterial oxyhemoglobin saturation.

patients who presented normal nocturnal BP dipping did not change between the control and CPAP groups for systolic BP (study entry: 31% and 13%, $P = .45$; after 6 months: 47% and 16%; $P = .11$, respectively) and for diastolic BP (study entry: 63% and 56%, $P = 1.00$; after 6 months: 58% and 32%, $P = .23$, respectively). Changes in BP did not correlate with CPAP compliance or with baseline symptoms of excessive daytime sleepiness as evaluated by the Epworth Sleepiness Scale. Interestingly, the BP changes were observed only while patients were awake, but not during nocturnal ABPM (Δ: $+2.8 \pm 4.5/+1.8 \pm 3.5$ mm Hg vs $+1.6 \pm 3.5/+0.8 \pm 2.9$ mm Hg, P = NS) (Figs 2, 3). At study end, two of the 16 patients assigned to control (12%) and six of the 19 patients assigned to CPAP (32%) controlled office BP (< 140/90 mm Hg) ($P = .18$). ABPM normalized in one patient (6%) in the control group and in three patients (16%) randomized to CPAP ($P = .61$). Biochemical variables (including aldosterone levels) at study entry and termination did not change significantly in the control or the CPAP group (e-Table 1).

Discussion

To our knowledge, this is the first study specifically designed to investigate the effects of OSA treatment on BP in patients with true resistant HTN. We found that CPAP therapy promoted a significant mean reduction of 6.5 mm Hg and 4.5 mm Hg for daytime systolic and diastolic BP, respectively. Our study, therefore, stresses the importance of recognizing and treating OSA in patients with true resistant HTN.

The impact of OSA treatment with CPAP on BP has been investigated extensively in the past 2 decades. In contrast to initial studies that suggested a marked

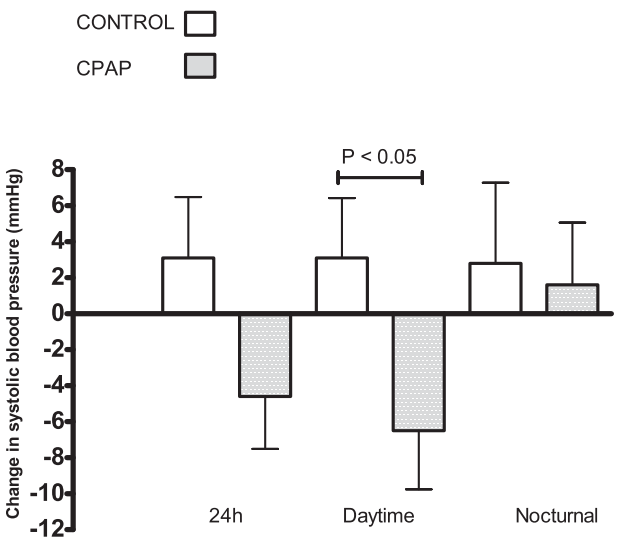

Figure 2. Effect of CPAP treatment on systolic BP in ambulatory BP. Data are presented as mean (SEM).

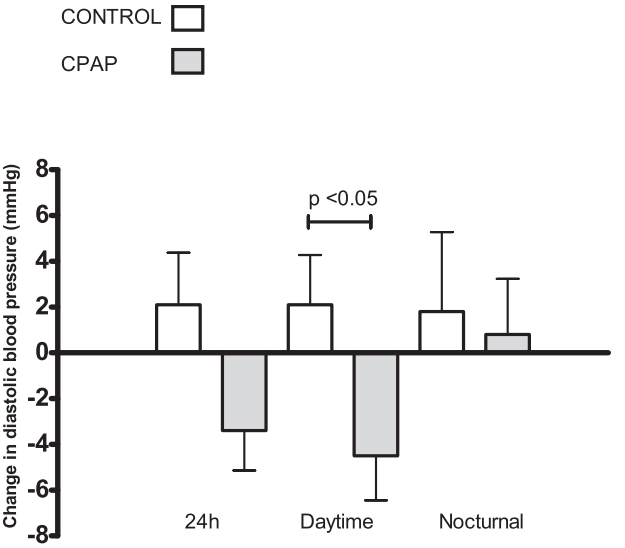

Figure 3. Effect of CPAP treatment on diastolic BP in ambulatory BP. Data are presented as mean (SEM).

fall in BP,[5,20] at least three meta-analyses have suggested a modest effect of CPAP on BP (around 2.5 mm Hg for systolic and 2 mm Hg for diastolic BP).[21-23] However, patients with resistant HTN were not included because of the lack of randomized trials at that time. A few nonrandomized studies consistently showed that the treatment of OSA in patients with resistant HTN resulted in reductions mainly in systolic BP (from 5.2 to 11 mm Hg).[5,9,10] Lozano and colleagues[11] performed a 3-month randomized trial in 64 patients with HTN and OSA and found no significant fall in ABPM after CPAP when the entire population was analyzed. A post hoc analysis of a subgroup of 41 patients with resistant HTN showed that CPAP promoted a significant reduction only in 24-h diastolic BP (−4.9 mm Hg).[11]

Our study has several design particularities that must be highlighted. First, in contrast to the previous study, the current investigation was designed primarily to study patients with resistant HTN. Second, there is growing evidence that a large number of patients who are considered to present resistant HTN in clinical practice are in fact not compliant with medications.[24] To this end, we monitored medication adherence carefully. Third, our follow-up was twice as long as the previous one (6 months). Our study is, therefore, in line with previous evidence and, to the best of our knowledge, is the first randomized investigation to show a significant fall in both systolic and daytime diastolic ABPM after CPAP in patients with OSA and true resistant HTN. The lack of a significant reduction in nocturnal BP is surprising and against our initial hypothesis. The subanalysis of Lozano and colleagues'[11] study of patients with resistant HTN also showed no significant reductions in nighttime ABPM. The precise reasons for these intriguing and contraintuitive results

are not clear. One possibility is that resistant HTN is a hyperadrenergic condition that contributes to sleep disruption and poor BP control during sleep,[25,26] independent of OSA. Recurrent arousals produced by repetitive BP measurements during the night may also contribute to this phenomenon. This hypothesis would lessen the importance of treating OSA in this population for the purpose of BP control.

A significant proportion of patients randomized to CPAP did not present full BP control based on the standard cutoffs defined in the guidelines. This result can be explained by the fact that the mean office systolic BP was relatively high at study entry, making it more difficult to achieve full BP control with any single intervention. The apparently modest BP reduction achieved by CPAP should not be interpreted as a disappointing result. HTN is a complex disease, and several mechanisms, such as genetic background, obesity, a sedentary lifestyle, and stress, contribute to the genesis of HTN. Therefore, it is unlikely that any single intervention will normalize BP among patients with resistant HTN. Consistent with this concept, the correction of other well-established causes of secondary HTN does not necessarily control or even cause a significant drop in BP among patients with HTN. For instance, in the Revascularization vs Medical Therapy for Renal-Artery Stenosis (ASTRAL) study,[27] BP control after revascularization plus medical therapy was not better than after medical therapy alone in patients with renovascular disease. In patients with resistant HTN taking three antihypertensive medications, a recent randomized study[28] showed that the addition of spironolactone caused a BP reduction similar to that observed in our study. Finally, a previous meta-analysis showed that a substantial part of the antihypertensive drug benefit in reducing fatal and nonfatal cardiovascular outcomes was already achieved by modest 5-mm Hg differences in systolic BP.[29] Therefore, the 6.5-mm Hg drop after CPAP therapy observed in our study may have an impact on cardiovascular outcomes in patients with resistant HTN and OSA.

One previous study showed that OSA was not associated with excessive daytime sleepiness among patients with resistant HTN.[8] The lack of typical symptoms may help explain the low recognition of OSA in this population.[8] Our study extends this finding by showing that the treatment of OSA with CPAP resulted in only a marginal reduction on the Epworth Sleepiness Scale and that the effects of CPAP on BP were not related to changes in daytime somnolence. The current investigation also explored the potential impact of CPAP on aldosterone levels. Previous evidence suggested that aldosterone levels are increased in patients with HTN and OSA, compared with control subjects.[30] Moreover, it has been suggested that complex interaction occurs between OSA, aldosterone, and resistant HTN. For instance, in patients with resistant HTN, aldosterone levels correlated with the severity of OSA.[31] As in a previous investigation,[32] OSA treatment with CPAP did not decrease aldosterone levels in our study. Therefore, the impact of OSA on aldosterone levels, as well as the relative contribution of aldosterone to BP dysregulation observed in patients with OSA, is still not clear.

Our study has some limitations. First, the number of patients included was relatively small. However, we used unique and stringent criteria. The run-in period resulted in the exclusion of a large number of patients due to poor adherence to the antihypertensive drugs. The current study was, therefore, able to isolate the effects of the treatment of OSA with CPAP on BP control in patients with true resistant HTN. Second, the control arm did not undergo a placebo treatment. On the other hand, sham-CPAP, the most common placebo advocated, may cause some discomfort and poor adherence, which potentially contributes to a rise in BP.[33] Third, the lack of blinding may have had an impact on the outcomes of the trial. However, the main outcome (24-h ABPM) was analyzed in a blind fashion.[34] Fourth, although BMI did not change along the study period, patients randomized to CPAP were heavier. However, BMI did not change across the study. Moreover, the BMI imbalance at baseline would have had a negative influence on the CPAP-treated group and therefore does not affect the interpretation of our results. Finally, we did not evaluate sodium intake, a potential contributor to resistant HTN, during the study.[1]

Conclusions

In conclusion, treating OSA with CPAP promoted significant daytime BP reductions in patients with true resistant HTN. The BP fall after CPAP is in the same range as that observed after recognition and treatment of other well-established causes of secondary HTN. The importance of our findings is highlighted by the fact that OSA is extremely common among patients with resistant HTN and is largely underrecognized. Future studies are necessary to clarify the impact of the treatment of OSA on other cardiovascular outcomes, such as target organ damage, in patients with resistant HTN.

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Dr Pedrosa: contributed to the study design, data collection and analysis, and writing the manuscript.
Dr Drager: contributed to the study design, data analysis, and drafting and writing of the manuscript.
Ms de Paula: contributed to the data collection and editing of the manuscript.

Ms Amaro: contributed to the data collection and editing of the manuscript.
Dr Bortolotto: contributed to the data collection and analysis and editing of the manuscript.
Dr Lorenzi-Filho: contributed to the study design, data analysis, and drafting and editing of the manuscript.
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