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The Antihypertensive Effect of Positive Airway Pressure on Resistant Hypertension of Patients with Obstructive Sleep Apnea: A Randomized, Double-Blind, Clinical Trial

To the Editor:

Resistant hypertension has been recognized as an additional risk in patients with hypertension, leading to an almost 1.5-fold increased risk of cardiovascular events among that population (1). Patients with obstructive sleep apnea (OSA) have almost five times higher risk of having resistant hypertension (2). Studies that evaluated the impact of treatment of OSA on blood pressure (BP) control among patients with resistant hypertension have some distinct methodological limitations, and none have included a sham positive airway pressure (PAP) control group (3–9).

The aim of this study was to evaluate the effect of PAP on BP measured by 24-hour ambulatory BP (ABP) monitoring of patients with true resistant hypertension. Some of the results of our trial have previously been reported in the form of an abstract (10).

All participants signed informed consent for participation. The protocol was registered in clinicaltrials.gov (NCT00929175). Patients between 30 and 70 years of age were screened in our Hypertension Outpatient Clinic (Porto Alegre, Brazil). True resistant hypertension was defined as an office BP of 140/90 mm Hg or greater in two visits, despite treatment with three or more drugs at adequate doses, including a diuretic, with adherence to treatment and without white coat phenomenon. Adherence was characterized when patients answered "no" to all questions of the Morisky-Green questionnaire (11). Office BP was measured with an aneroid sphygmonanometer (Tycos; Welch Allyn, Skaneateles Falls, NY). ABP monitoring was performed using a Spacelabs monitor (model 90207; Spacelabs, Redmond, WA). BP was measured every 20 minutes from 7:00 A.M. to 11:00 P.M. and every 30 minutes from 11:00 P.M. to 7:00 A.M. We considered an examination adequate if 80% or more of the measurements were valid. Hypertension on ABP monitoring was defined as a mean 24-hour BP of 130/80 mm Hg or greater.

The sleep study was performed with a type 3 portable monitoring device (Somnocheck; Weinmann GmbH, Hamburg, Germany), which was validated by our service (12). The examination was conducted at home. Recordings of artifact-free tracings shorter than 4 hours were discarded, and the examination was repeated. The apnea–hypopnea index was defined according to standard criteria (13).

Patients were randomized to active PAP or sham PAP for 8 weeks, in a 1:1 proportion in blocks of four, and stratified by systolic BP on 24-hour ABP monitoring. The active PAP (Remstar-Auto; Respironics, Murraysville, PA) was set to operate with pressures from +6 to +12 cm H_2O. The sham PAP used the same equipment fixed at the lowest pressure (4 cm H_2O) and modified, as recommended by Farré and colleagues (14), to cause a leak that reduced the mask pressure to 1 cm H_2O as certified by manometer gauging. Both groups received the same instructions about the use of PAP and an operation manual with answers to the most frequent queries.

In the first 48 hours after randomization, patients were contacted to verify if the device worked, and, at the end of the first week, patients were visited at home to verify the operation and read the memory card. By the end of 8 weeks, participants underwent the second 24-hour ABP monitoring.

The sample size was calculated to detect an effect size of 10 mm Hg in 24-hour systolic ABP monitoring with a standard deviation of 12 mm Hg and a two-sided significance level of 5%.

Between February 2008 and April 2013, 47 of 538 consecutive patients screened for resistant hypertension, and with at least moderate OSA, were randomized to active PAP or sham PAP. Two patients abandoned the active PAP group, resulting in a final sample of 45 patients. The groups were roughly similar in their baseline characteristics (Table 1). Table E1 in the online supplement shows the medications and mean doses used by patients in both groups. There were no changes in the prescribed medications during the trial. Table E2 shows that the patients' adherence to the active and sham intervention was not substantially different.

Figure 1 shows that there was a significant decrease in 24-hour systolic ABP monitoring in the active versus the sham PAP group, with between-group deltas of BP variation, respectively, of 10 mm Hg (95% confidence interval [CI] = 3.8–16.2) versus 0.7 mm Hg (95% CI = −5.3 to 6.7) (P = 0.035). The reduction of diastolic BP did not reach formal statistical significance. Patients treated with active PAP had greater reductions in office diastolic BP than patients in the control group, with a between-group delta

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This letter has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Clinical trial registered with www.clinicaltrials.gov (NCT00929175).

Table 1. Baseline Characteristics of the Study Participants according to Treatment Group

Variable	Sham PAP (*n* = *23*)	Active PAP (*n* = *24*)	Total (*n* = *47*)
Male sex, %	13 (57)	14 (58)	27 (57)
Age, yr	59.2 ± 8.3	59.5 ± 7.3	59.4 ± 7.7
Smokers, %	6 (26)	7 (29)	13 (27)
BMI, kg/m^2	29.4 ± 4.6	30.2 ± 4.3	29.8 ± 4.4
Neck circumference, cm	40 ± 3.6	40 ± 3.4	40 ± 3.5
Waist, cm	102 ± 10.4	104 ± 10.7	102.9 ± 10.5
ESS*	10 (6–15)	10 (6–17)	10 (6–15)
Drugs in the baseline	4 ± 1	4 ± 1	4 ± 1
Office systolic BP, mm Hg	165 ± 17	165 ± 23	165 ± 20
Office diastolic BP, mm Hg	96 ± 15	96 ± 17	96 ± 16
Heart rate	69 ± 9	69 ± 9	69 ± 9
AHI, events/h*	20 (17–37)	20.5 (18–26)	20 (18–31)
SBP—24 h, mm Hg	146 ± 16	150 ± 18	148 ± 17
DBP—24 h, mm Hg	88 ± 13	88 ± 12	88 ± 13
SBP—daytime, mm Hg	148 ± 18	153 ± 20	151 ± 19
DBP—daytime, mm Hg	90 ± 14	91 ± 14	91 ± 14
SBP—nighttime, mm Hg	139 ± 12	140 ± 15	139 ± 14
DBP—nighttime, mm Hg	81 ± 10	81 ± 10	81 ± 10
Comorbidities			
Diabetes type 2, %	7 (30.4)	6 (25)	13 (27.6)
Hypothyroidism, %	3 (13)	0 (0)	3 (6.3)
Atrial fibrilation, %	1 (4)	2 (8)	3 (6.3)
Heart faillure, %	1 (4.3)	0 (0)	1 (2.1)
Ischemic cardiopathy, %	4 (17.3)	3 (12.5)	7 (14.8)
Stroke, %	2 (8.6)	1 (4)	3 (6.3)

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; BP = blood pressure; DBP = diastolic BP; ESS = Epworth sleep sclale; PAP = positive airway pressure; SBP = systolic BP.
Values presented are means ± SD or percentages, unless otherwise noted.
*Median (interquartile range).

of 7.1 mm Hg (95% CI = 0.5–13; $P = 0.035$). The corresponding between-group adjusted delta of systolic BP was 5.0 mm Hg (95% CI = −17 to 7; $P = 0.431$).

The magnitude of the BP-lowering effect, 9.3 mm Hg for systolic BP, may lead to a substantial reduction in the incidence of cardiovascular events, such as fatal and non-fatal stroke and myocardial infarction (15, 16). The effect size of the main studies that evaluated the effect of PAP on BP of patients with resistant hypertension (3–7) has been shown to vary from 4.6 to 11 mm Hg in systolic BP during 24-hour, daily, or nightly periods of monitoring. Three of these studies were nonrandomized (3–5), and the main findings of the other two were restricted to subgroups (6, 7). The study by Pedrosa and colleagues (8) was the first to enroll patients with resistant hypertension instead of those with OSA, but did not employ a sham continuous PAP control. The Hipertensión Arterial Resistente Control con CPAP trial (HIPARCO) (9) found a somewhat lower effect of the PAP intervention, which was significant for 24-hour mean and diastolic BP. Due to its multicenter design and higher statistical power, these estimates of efficacy may be more precise. Nonetheless, there are some important differences between that trial design and ours, such as the use of sleep laboratory versus home sleep studies, the use of sham PAP in our study, and the different methods of evaluating adherence. Our patients could have more severe and true resistant hypertension, as they were older, had higher ABP, and were using more BP-lowering drugs at baseline. In the HIPARCO trial, of 266 patients assessed for eligibility, 194 were randomized (72%). The corresponding figures in our trial were 538 patients assessed for eligibility and 43 randomized (8.7%). It is of note that 151 patients were excluded after dose adjustment in the run-in phase of our study.

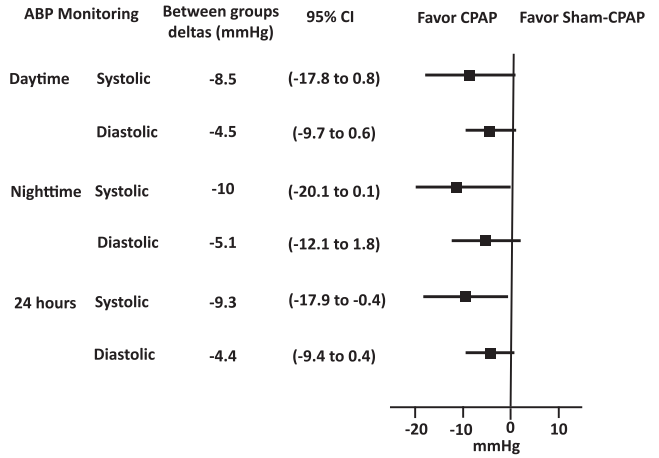

Figure 1. Deltas between blood pressure (BP) variation in the active positive airway pressure (PAP) and sham PAP groups. CI = confidence interval; CPAP = continuous positive airway pressure.

The sample size may explain the marginal significance in our trial. We reached the originally planned sample size, but the variance of BP was higher than expected. The 2-month intervention period precludes conclusions on the persistence of the BP-lowering effect or on further BP-lowering effect if PAP

were used for longer periods. The single-center study reduces the generalization of findings. Among the strengths of our study are the double-blinded sham PAP controlled design, the inclusion of patients with true resistant hypertension, and the measurement of BP by ABP monitoring. The screening of patients in a hypertension clinic and not in a sleep clinic increases the external validity and the applicability of our findings, as it reproduces the main clinical problem faced by clinicians and cardiologists.

In conclusion, treatment with PAP promotes a significant reduction of ABP in patients with true resistant hypertension and at least moderate OSA. The magnitude of the benefit should be investigated in studies with larger sample sizes and in meta-analysis of this and other randomized controlled trials. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Does Inspiratory Muscle Dysfunction Predict Readmission after Intensive Care Unit Discharge?

To the Editor:

Dysfunction of peripheral and respiratory muscles acquired in the intensive care unit (ICU) is associated with poor outcome, including delayed weaning from mechanical ventilation (1). Controlled mechanical ventilation can result in diaphragm atrophy (2), and critical illness polyneuromyopathy can also involve respiratory muscles (1). Diaphragm dysfunction may exist upon ICU admission and is associated with ICU and hospital mortality (3). However, the prevalence and impact of inspiratory muscle dysfunction in patients who have survived an episode of acute hypercapnic respiratory failure (AHRF) in the ICU have not been reported to date.

In the present study, we performed a prospective follow-up of all patients recovering from an episode of AHRF after ICU discharge and measured sniff nasal inspiratory pressure (Pnas) at Day 7 after ICU discharge. We recorded readmissions for respiratory causes to the general wards and to the ICU during a 6-week period after ICU discharge. Sniff Pnas was performed according to the American Thoracic Society/European Respiratory Society recommendations (4). The 5th percentile Pnas value of a healthy population of the same age and gender was used as a cut-off value for inspiratory

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