CHEST

Longitudinal Effect of CPAP on BP in Resistant and Nonresistant Hypertension in a Large Clinic-Based Cohort

Harneet K. Walia, MD; Sandra D. Griffith, PhD; Nancy Foldvary-Schaefer, DO; George Thomas, MD; Emmanuel L. Bravo, MD; Douglas E. Moul, MD, MPH; and Reena Mehra, MD, FCCP

BACKGROUND: Clinic-based effectiveness studies of sleep-disordered breathing (SDB) treatment in reducing BP in resistant hypertension (RHTN) vs non-RHTN are sparse. We hypothesize that CPAP use in SDB reduces BP significantly in RHTN and non-RHTN in a large clinic-based cohort.

METHODS: Electronic medical records were reviewed in patients with SDB and comorbid RHTN and non-RHTN for CPAP therapy initiation (baseline) and subsequent visits. We estimated generalizable BP changes from multivariable mixed-effects linear models for systolic BP (SBP), diastolic BP, and mean arterial pressure, adjusting for RHTN status, age, sex, race, BMI, cardiac history, and diabetes and repeated measure correlation.

RESULTS: Of 894 patients, 130 (15%) had RHTN at baseline (age, 58 $\pm$ 12 years; 52% men; BMI, 36 $\pm$ 9 kg/m^2). Patients with RHTN had significantly higher BP overall ($P < .001$), most notably for SBP (6.9 mm Hg; 95% CI, 3.84, 9.94). In the year following CPAP initiation, improvements in BP indexes did not generally differ based on RHTN status in which RHTN status was a fixed effect. However, there was a significant decrease in SBP (3.08 mm Hg; 95% CI, 1.79, 4.37), diastolic BP (2.28; 95% CI, 1.56, 3.00), and mean arterial pressure (2.54 mm Hg; 95% CI, 1.73, 3.36) in both groups.

CONCLUSIONS: In this clinic-based effectiveness study involving patients closely followed for BP control, a significant reduction of BP measures (strongest for SBP) was observed in response to CPAP which was similar in RHTN and non-RHTN groups thus informing expected clinical CPAP treatment response. CHEST 2016; 149(3):747-755

KEY WORDS: hypertension; sleep-disordered; sleep medicine

ABBREVIATIONS: AHI = apnea-hypopnea index; AIC = Akaike Information Criteria; DBP = diastolic BP; EMR = electronic medical record; HTN = hypertension; KP = Knowledge Program; MAP = mean arterial pressure; RHTN = resistant hypertension; SBP = systolic BP; SDB = sleep-disordered breathing; SDC = Sleep Disorders Center

AFFILIATIONS: From the Sleep Disorders Center (Drs Walia, Foldvary-Schaefer, Moul, and Mehra), Neurological Institute, Department of Quantitative Health Sciences (Dr Griffith), and Department of Nephrology and Hypertension (Drs Thomas and Bravo), Cleveland Clinic, Cleveland, OH.

Part of this article has been presented at the Associated Professional Sleep Societies 28th Annual Meeting, May 31-June 4, 2014, Minneapolis, MN, and published in abstract form (Walia HK, Griffith SD, Thomas G, et al. *Sleep*. 2014;37(suppl):A109. Abstract 0304).

FUNDING/SUPPORT: This study was funded by the National Heart, Lung, and Blood Institute (NHLBI) [R21HL108226 and R01HL109493] and a Cleveland Clinic Neurological Institute-Core Scholar Award.

CORRESPONDENCE TO: Harneet K. Walia, MD, Center for Sleep Disorders, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195; e-mail: waliah@ccf.org

DOI: http://dx.doi.org/10.1378/chest.15-0697

Hypertension (HTN), including resistant hypertension (RHTN), represents an enormous economic burden to society[1,2] with an estimated 3% to 30% of patients with HTN also suffering from RHTN.[3,4] RHTN is defined as BP that remains above goal (140/90 mm Hg) despite simultaneous use of three classes of antihypertensive agents including a diuretic, or controlled BP with use of at least four antihypertensive medication classes.[5] In the past decade, while the prevalence of HTN has remained stable, there has been an approximate doubling of RHTN prevalence.[6] Given the challenges and complexities in classification of true RHTN, "apparent" RHTN has become an increasingly used term and therefore in this manuscript, RHTN implicitly refers to apparent RHTN.[7] Considering the key role of sleep-disordered breathing (SDB) in the etiopathogenesis of HTN, increase in RHTN is likely attributable to the increased prevalence in SDB. As HTN severity increases, the risks for cardiovascular events, stroke, and death worsen compared with individuals with controlled HTN.[8,9]

Clinical data suggest an association between SDB and RHTN.[10] Potential mechanisms include endothelial dysfunction[11] and activation of the renin-angiotensin-aldosterone system.[12-15] Additionally, increased sympathetic activity, changes in autonomic cardiovascular modulation, increased systemic inflammation and increased chemo reflex drive, and increased rostral edema contribute to increases in BP, including rises that are refractory to standard medication treatment.[16-19] Randomized clinical trials have demonstrated modest antihypertensive benefits of treatment of SDB with CPAP, with mild reductions in BP of 3 to 5 mm Hg[20,21] compared with more substantive reductions in RHTN, namely 7 to 10 mm Hg.[22] Notwithstanding the vast interventional trial data published on SDB and HTN, relatively fewer randomized studies[23-25] have investigated the effect of CPAP on control of BP in patients with OSA and RHTN, and none have examined the effect of CPAP in real-world clinical practice settings.[22,26,27] The limited data available in the "real-world" clinical practice setting suggests a reduction in mean arterial pressure (MAP) in a small sample of patients with resistant hypertension, and a negligible effect on hypertensive patients with controlled BP.[28]

We, therefore, chose to leverage an existing large, clinic-based cohort to investigate the effect of CPAP on BP in patients with RHTN vs non-RHTN presenting to a large tertiary care sleep medicine clinic. We hypothesize that CPAP use in SDB will reduce BP significantly in RHTN and non-RHTN, and the effect will be more pronounced in RHTN, even after consideration of confounders. Additionally, given data implicating the preferential role of rostral neck edema specifically in RHTN compared with HTN,[19] we anticipate that neck circumference used in place of BMI will more accurately characterize the anthropometric risk in RHTN.

Materials and Methods

Study Procedures

Study Sample: Electronic medical record (EMR) data extraction was performed for patients ≥ 18 years of age presenting for outpatient visits in the Cleveland Clinic Sleep Disorders Center (SDC) from January 7, 2010, to July 16, 2013. Patient confirmation of HTN and SDB was based on physician diagnosis and self-reported use of CPAP therapy for SDB collected through the Cleveland Clinic's Knowledge Program (KP), an electronic system for systematically collecting patient-reported outcomes at outpatient clinic visits. Patients with the most common causes of secondary HTN including chronic renal disease, primary hyperaldosteronism, Cushing syndrome, renal artery stenosis, or a combination were excluded. Comorbid conditions were extracted based upon physician completion or ICD billing code.

We defined the baseline visit as the last SDC visit in which the patient indicated that there had been no CPAP usage. The date of CPAP initiation was based on change to the affirmative from the baseline clinic visit for a patient-reported question regarding CPAP therapy collected by the KP. Baseline demographic and clinical data included age, sex, race, history of diabetes, and history of cardiac comorbidities (ie, cardiovascular disease, peripheral vascular disease, coronary heart disease, heart failure, or stroke). Sleep study data including the apnea-hypopnea index (AHI) were obtained from polysomnography and combined with EMR data to obtain baseline BMI (kg/m^2) and neck circumference (cm). Antihypertensive medication usage (indicated as active in the EMR), BP, and self-reported CPAP adherence were extracted for the baseline visit and all subsequent SDC visits in the following year. Antihypertensive medications were grouped as follows: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, dihydropyridine or nondihydropyridine calcium channel blockers, central α agonists, direct vasodilators, diuretics, peripheral α blockers, and renin inhibitors. Combination antihypertensive medications were allocated to multiple discrete classes based on components. We defined baseline RHTN as per the American Heart Association scientific statement[5]; that is, BP that remains above goal (140/90 mm Hg) despite simultaneous use of three classes of antihypertensive agents including a diuretic, or controlled BP with use of at least four antihypertensive medication classes. Patients without RHTN comprised the non-RHTN group. The study was approved by Institutional Review Board of the Cleveland Clinic (number 12-967).

Polysomnography: Polysomnography was performed according to standard guidelines[29] using a Nihon Kohden system, version 8 (Nihon Kohden Corporation). Hypopneas were defined as ≥ 50% reduction of airflow in the nasal pressure channel for ≥ 10 s resulting in an arousal or ≥ 3% oxygen desaturation.[29] The recording montage included EEG

(F3-M2, C3-M2, O1-M2, F4-M1, C4-M1, O2-M1), bilateral electrooculography, submental and bilateral anterior tibialis electromyography, position sensor, ECG, thoracic and abdominal respiratory inductance plethysmography, and finger pulse oximetry. Nasal airflow and nasal pressure was measured using an oronasal thermistor and nasal cannula respectively.

BP Measurement: BP measurements were obtained in the outpatient setting in the SDC by a medical assistant using an automatic cuff according to standard clinical procedure, that is, in the sitting position with the patient relaxed, legs uncrossed, and the arm maintained at the level of the heart (Automated Dynamat, Dinamap Procare Monitor; GE Medical System).

KP System: The Cleveland Clinic KP[30] is an independent electronic outcomes measurement and archival system that is also embedded within the EMR. Pertinent health status measures in the SDC measurement ensemble include questions regarding the usage of CPAP and the self-report of the number of days and hours of usage. The Centers for Medicare and Medicaid Services define CPAP adherence as $\geq$ 5 d/wk and $\geq$ 4 h/d of self-reported CPAP use.[31]

Statistical Analysis: We calculated descriptive statistics for each baseline variable stratified by HTN group. We tested for differences in baseline variables between the RHTN and non-RHTN groups using Wilcoxon (continuous variables) and Fisher exact tests (categorical variables).

Primary Analysis: We examined the association between CPAP therapy and change in BP using linear mixed-effects models that account for the varying numbers of follow-up days between patients when analyzing BP measurements. The models included BP outcome variables such as systolic BP (SBP), diastolic BP (DBP), or MAP ([2 $\times$ DBP) + SBP]/3) and predictors included an indicator for pre/post-CPAP initiation, HTN group, and other clinically relevant baseline variables including age, sex, race, BMI, cardiac, and diabetes history. We included normally distributed subject-specific random effects at the patient level to account for correlation between repeated measurements within the same patient, considering both random intercepts and slopes specifications. Fixed effects were included for all other variables. To test whether the difference in BP from baseline averaged over the follow-up period differed between the RHTN and non-RHTN groups, we tested a fixed-effect interaction term between pre/post-CPAP and HTN group to address the primary hypothesis. We also tested a fixed effect interaction term between pre/post-CPAP and controlled and uncontrolled BP in the RHTN group to assess for differential effects of CPAP on BP outcomes in these groups.

Secondary Analysis: There are data suggesting that neck size is a predictor for SDB[32] and may serve as a surrogate for rostral fluid displacement which bears biologic plausibility in the pathogenesis of SDB and RHTN.[19] We, therefore, considered the impact of substituting neck size for BMI in the multivariable model to examine for superiority of fit. We noted changes in model coefficients and significance and compared model fit using Akaike Information Criteria (AIC) with a better fitting model defined as two or more units lower than the comparison model.[33]

As AHIs were not available for the patients who underwent sleep studies at facilities other than Cleveland Clinic, we examined models including AHI in the subset of patients with available data. We performed sensitivity analysis to assess the robustness of the primary analysis in terms of CPAP adherence only on patients who self-reported as CPAP adherent, which included baseline visits for all patients with at least one visit reporting adherence data, but only considered follow-up visits when adherence was reported. All statistical analyses were performed using R, version 3.1.1,[34] and P values $\leq$ .05 were considered statistically significant.

Results

Baseline Characteristics

We analyzed 894 of 1,000 (89%) eligible patients with HTN who had complete data from their visit at the Cleveland Clinic SDC during the study period (Table 1). Generally, patients with missing RHTN status had similar demographic characteristics to those with complete data but tended to be slightly younger (49 $\pm$ 14 years, $P < .001$); have increased neck size, 42 ($\pm$ 5) cm; less history of diabetes, 88 (86%) and cardiac comorbidities, 93 (91%); and higher MAP, 99 ($\pm$ 11) mm Hg, and DBP, 81 ($\pm$ 10) mm Hg. Among patients with complete and available RHTN status, 130 (15%) were RHTN positive at baseline (98 patients with controlled BP [75.4%] and 32 [24.6%] with noncontrolled BP) and the remaining 764 (85%) classified as non-RHTN. The mean age and BMI were significantly higher in the RHTN group compared with the non-RHTN group ($P = .02$ and $P = .007$, respectively) and the groups were balanced in terms of sex. A higher but nonsignificant percentage of African Americans were observed in the RHTN group compared with the non-RHTN group. The MAP and SBP at baseline were higher in the RHTN than the non-RHTN group ($P < .01$), whereas no significant difference was found for DBP.

Of the full dataset, 728 (81.4%) met the Centers for Medicare and Medicaid Services definition for self-reported CPAP adherence for at least one follow-up visit. Most demographic characteristics were similar between the adherent and nonadherent groups, although adherent patients were older, had higher AHI, were more likely to have a history of cardiac comorbidities, and had slightly lower MAP and DBP.

CPAP Effect on Change in BP Indexes in RHTN and Non-RHTN

Primary Analysis: A small and nonstatistically significant interaction term was observed between post-CPAP and RHTN in all models indicating reduction in BP was not different between the RHTN and non-RHTN groups. Thus, this term was excluded from the final model.

In fully adjusted models, in the year following CPAP initiation, there was a significant decrease in SBP

TABLE 1] Descriptive Statistics at Baseline

Descriptive Statistics	Total	Non-RHTN	RHTN	*P* Value[a]
No.	894	764 (85%)	130 (15%)	…
Age, mean (SD), y	58 (± 12)	58 (± 12)	61 (± 12)	.002
Sex				
Female	430 (48)	367 (48)	63 (48)	1.0
Race				.072
African American	225 (25)	178 (23)	47 (36)	
Asian/Pacific Islander	7 (1)	7 (1)	0 (0)	
Caucasian	642 (72)	561 (73)	81 (62)	
Declined	3 (0)	3 (0)	0 (0)	
Multiracial	5 (1)	4 (1)	1 (1)	
Native Hawaiian/Pacific Islander	1 (0)	1 (0)	0 (0)	
Unknown/unavailable	11 (1)	10 (1)	1 (1)	
BMI, mean (SD), kg/m^2	36 (± 9)	36 (± 9)	38 (± 9)	.007
Neck size, mean (SD), cm	41 (± 5)	41 (± 5)	42 (± 5)	.120
Tobacco history				.059
Current	42 (5)	40 (5)	2 (2)	
Former	212 (24)	172 (23)	40 (31)	
Never	237 (27)	200 (26)	37 (28)	
AHI, median (IQR)	29 (15-54)	29 (15-52)	33 (17-63)	.063
Diabetes history	228 (26)	181 (24)	47 (36)	.003
Cardiac history	185 (21)	143 (19)	42 (32)	< .001
Medication classes				
Median (IQR)	2 (1-3)	2 (1-2)	4 (4-4)	< .001
ACE inhibitors	433 (48)	344 (45)	89 (68)	< .001
Angiotensin receptor blockers	184 (21)	127 (17)	57 (44)	< .001
β-Blockers	405 (45)	299 (39)	106 (82)	< .001
CCB (dihydropyridine)	207 (23)	132 (17)	75 (58)	< .001
CCB (nondihydropyridine)	72 (8)	49 (6)	23 (18)	< .001
Central α agonists	30 (3)	11 (1)	19 (15)	< .001
Direct vasodilators	43 (5)	17 (2)	26 (20)	< .001
Diuretics	540 (60)	410 (54)	130 (100)	< .001
Peripheral α blockers	33 (4)	17 (2)	16 (12)	.002
Renin inhibitors	3 (0)	2 (0)	1 (1)	.38
BP				
Mean arterial pressure, mean (SD)	97 (± 13)	96 (± 12)	100 (± 17)	.004
Systolic BP, mean (SD)	135 (± 20)	134 (± 19)	141 (± 25)	< .001
Diastolic BP, mean (SD)	77 (± 11)	77 (± 11)	79 (± 15)	.098
Follow-up after initial visit, median (IQR), d	126 (77-273)	122 (75-270)	156 (90-296)	.038
Total no. of visits, median (IQR)	2 (2-3)	2 (2-3)	3 (2-3)	.33

Data are given as No. (%) unless otherwise indicated. ACE = angiotensin-converting enzyme; AHI = apnea-hypopnea index; CCB = calcium channel blocker; IQR = interquartile range; RHTN = resistant hypertension.

[a]For continuous variables, *P* values correspond to Wilcoxon tests between RHTN groups. For categorical variables, *P* values correspond to Fisher exact tests between RHTN groups.

(3.08 mm Hg; 95% CI, 1.79, 4.37), DBP (2.28, 95% CI, 1.56, 3), and MAP (2.54 mm Hg; 95% CI, 1.73, 3.36). This improvement did not differ based on RHTN status, but patients with RHTN had higher BP indices overall (all $P < .001$) in the adjusted models, most notably for SBP (6.90 mm Hg; 95% CI, 3.84, 9.95) both before and

after CPAP initiation (Fig 1). Note that although the CIs of the predicted SBP overlap between non-RHTN and RHTN groups, the difference between groups is significantly different from zero ($P < .001$), as is also the case for MAP and DBP (Table 2). Patients with cardiac history had lower BP profiles and patients with diabetes and increasing age were associated with lower MAP and DBP. The interaction term of pre/post-CPAP and controlled and uncontrolled BP groups of RHTN was not statistically significant, thereby indicating no differential impact of CPAP on BP outcomes between the groups.

Secondary Analyses: Substituting neck size for BMI (Table 3) yielded a better fitting model, as measured by AIC (Table 4), with a slightly more pronounced reduction in BP after CPAP. In the fully adjusted model, there was a significant decrease in SBP (3.36 mm Hg; 95% CI, 2.03, 4.70), DBP (2.42; 95% CI, 1.68, 3.16), and MAP (2.73 mm Hg; 95% CI, 1.89, 3.57).

Among patients with AHI (757 patients, 85%), model results were similar to the primary analysis even after

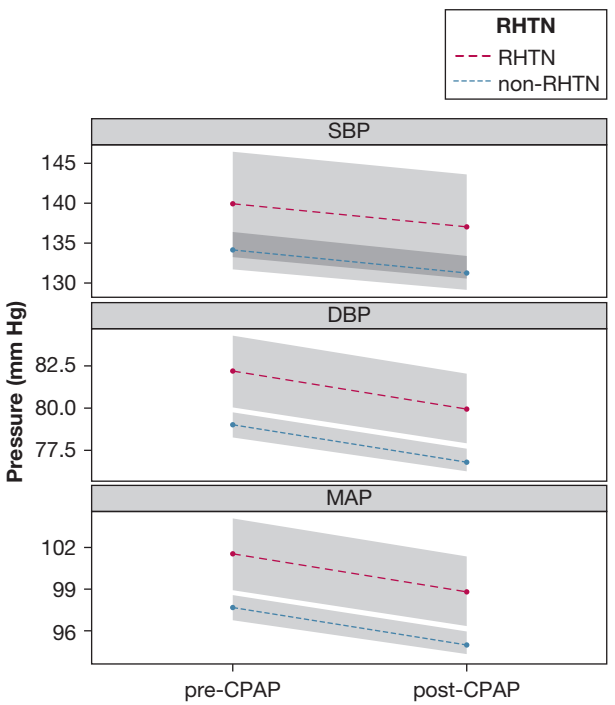

Figure 1 – *Predicted trends in BP indexes before and after initiation of CPAP therapy based on results from the fitted multivariable model. Lines represent population-averaged model estimates, stratified by hypertension group. Shaded areas represent 95% prediction intervals for the fixed effects. Other covariate values are set to their respective medians and modes from the sample (Caucasian race, BMI equal to 36, male sex, no history of cardiac or diabetic comorbidities, and 58 y of age). DBP = diastolic BP; MAP = mean arterial pressure; RHTN = resistant hypertension; SBP = systolic BP.*

TABLE 2] Change in BP Indexes in RHTN and Non-RHTN Groups With CPAP

Variable	Mean Arterial Pressure		Systolic BP		Diastolic BP	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
(Intercept)	107.14 (101.55, 112.73)	< .001	128.78 (119.99, 137.57)	< .001	96.33 (91.38, 101.28)	< .001
Post-CPAP	−2.54 (−3.36, −1.73)	< .001	−3.08 (−4.37, −1.79)	< .001	−2.28 (−3, −1.56)	< .001
RHTN	4.71 (2.76, 6.65)	< .001	6.9 (3.84, 9.95)	< .001	3.61 (1.89, 5.33)	< .001
Sex (male vs female)	1.45 (0.03, 2.86)	.045	−0.28 (−2.51, 1.94)	.804	2.31 (1.06, 3.56)	< .001
Race (Caucasian vs non-Caucasian)	−2.01 (−3.6, −0.41)	.014	−2.28 (−4.78, 0.23)	.075	−1.87 (−3.28, −0.46)	.009
BMI	0.02 (−0.07, 0.1)	.71	0.19 (0.06, 0.32)	.006	−0.07 (−0.14, 0)	.067
Cardiac history	−3.39 (−5.1, −1.68)	< .001	−4.57 (−7.26, −1.88)	.001	−2.8 (−4.31, −1.28)	< .001
Diabetic history	−1.19 (−2.78, 0.41)	.144	0.46 (−2.04, 2.97)	.716	−2.01 (−3.42, −0.6)	.005
Age	−0.17 (−0.24, −0.11)	< .001	0.01 (−0.09, 0.12)	.778	−0.27 (−0.32, −0.21)	< .001

Results from multivariable model including all patients. See Table 1 legend for expansion of abbreviations.

TABLE 3] Change in BP Indexes in RHTN and Non-RHTN Groups With CPAP (Substituting Neck Size as a Predictor in Place of BMI)

Variable	Mean Arterial Pressure		Systolic BP		Diastolic BP	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
(Intercept)	100.28 (91.91, 108.65)	< .001	114.88 (101.76, 128)	< .001	92.98 (85.54, 100.42)	< .001
Post-CPAP	−2.73 (−3.57, −1.89)	< .001	−3.36 (−4.7, −2.03)	< .001	−2.42 (−3.16, −1.68)	< .001
RHTN	4.48 (2.5, 6.46)	< .001	7.05 (3.94, 10.16)	< .001	3.19 (1.43, 4.96)	< .001
Sex (male vs female)	0.55 (−1.11, 2.21)	.515	−3.74 (−6.34, −1.14)	.005	2.7 (1.22, 4.17)	< .001
Race (Caucasian vs non-Caucasian)	−2.35 (−3.99, −0.7)	.005	−2.97 (−5.55, −0.4)	.024	−2.03 (−3.49, −0.57)	.007
Neck size, cm	0.18 (0, 0.36)	.045	0.55 (0.28, 0.83)	< .001	−0.01 (−0.16, 0.15)	.938
Cardiac history	−2.87 (−4.62, −1.11)	.001	−4.08 (−6.83, −1.33)	.004	−2.26 (−3.82, −0.7)	.005
Diabetic history	−1.14 (−2.77, 0.48)	.168	0.76 (−1.79, 3.3)	.559	−2.09 (−3.54, −0.65)	.005
Age	−0.16 (−0.22, −0.1)	< .001	0.02 (−0.08, 0.12)	.727	−0.25 (−0.31, −0.19)	< .001

See Table 1 legend for expansion of abbreviations.

TABLE 4] AIC for Models Including Either BMI or Neck Size as a Variable and Each BP Outcome

Variable	Mean Arterial Pressure	Systolic BP	Diastolic BP
BMI	16,342.20	18,285.50	15,810.81
Neck size	15,631.64	17,486.45	15,120.62

Lower AIC values indicate a better fitting model. AIC = Akaike information criteria.

adjustment for AHI. AHI was a significant predictor of BP; each one-unit increase in AHI was associated with higher levels of SBP (0.06 mm Hg; 95% CI, 0.02, 0.11), DBP (0.02; 95% CI, 0, 0.05), and MAP (0.04 mm Hg; 95% CI, 0.01, 0.06).

In sensitivity analyses, patients who were CPAP-adherent demonstrated a significant decrease in SBP (2.88 mm Hg; 95% CI, 1.46, 4.3), DBP (2.22; 95% CI, 1.43, 3.01), and MAP (2.44 mm Hg; 95% CI, 1.54, 3.34) compared with the overall cohort in fully adjusted models in the year following CPAP initiation. Additionally, in the CPAP adherent group, those with RHTN at baseline and at follow-up had a higher BP overall, most notably for SBP (5.79 mm Hg; 95% CI, 2.54, 9.04), consistent with the overall cohort findings (Table 5).

Discussion

The most striking observation emerging from our clinic-based 1-year follow-up large-scale patient study was a similar improvement in SBP, DBP, and MAP following CPAP initiation regardless of RHTN status. Additionally, we observed a pronounced reduction in SBP, responsible for driving the concordant improvement of MAP. The overall findings of BP improvements persisted even after exclusion of patients not adherent to CPAP. Data also suggested that neck size may provide a better sense of risk physiology compared with BMI.

While we expected to find an overall improvement in BP profiles in those with HTN and non-RHTN following CPAP adherence, we unexpectedly observed no differential BP improvement between RHTN and non-RHTN groups, contrasting a previous retrospective study demonstrating a significant BP reduction among non-RHTN patients, but not patients with RHTN.[28] Possible reasons for observed differences include a higher number of women with high cardiovascular risk in our study compared with the mostly male cohort in the previous study, highlighting the potential for

TABLE 5] Change in BP Indexes in Patients Adherent to CPAP

Variable	Mean Arterial Pressure		Systolic BP		Diastolic BP	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
(Intercept)	107.72 (101.65, 113.79)	< .001	127.98 (118.52, 137.43)	< .001	97.6 (92.18, 103.02)	< .001
Post-CPAP	−2.44 (−3.34, −1.54)	< .001	−2.88 (−4.3, −1.46)	< .001	−2.22 (−3.01, −1.43)	< .001
RHTN	4.04 (1.96, 6.13)	< .001	5.79 (2.54, 9.04)	< .001	3.17 (1.31, 5.04)	.001
Sex (male vs female)	1.74 (0.21, 3.28)	.026	0.04 (−2.35, 2.44)	.972	2.59 (1.22, 3.96)	< .001
Race (Caucasian vs non-Caucasian)	−2.64 (−4.41, −0.87)	.004	−2.98 (−5.74, −0.22)	.034	−2.46 (−4.04, −0.88)	.002
BMI	0 (−0.09, 0.1)	.926	0.18 (0.04, 0.33)	.013	−0.09 (−0.17, 0)	.045
Cardiac history	−3.83 (−5.69, −1.97)	< .001	−5.18 (−8.07, −2.28)	< .001	−3.16 (−4.82, −1.5)	< .001
Diabetic history	−1.87 (−3.62, −0.12)	.037	−0.8 (−3.53, 1.92)	.564	−2.4 (−3.96, −0.83)	.003
Age	−0.17 (−0.24, −0.1)	< .001	0.04 (−0.07, 0.15)	.444	−0.27 (−0.33, −0.21)	< .001

Results from multivariable model including only compliant patients. See Table 1 legend for expansion of abbreviations.

sex-specific or underlying cardiovascular risk modification of BP responses to CPAP intervention. Additionally, medical practice variations in prescribing type and dose of antihypertensive medications may account for such differences.[28] Also, in this patient population, there is a possibility that several of the patients in the RHTN group may be nonresistant to treatment. Previous randomized controlled trials have demonstrated an improvement in MAP, but not SBP, with CPAP treatment.[26] While we also observed a reduction in MAP of similar magnitude in response to CPAP, this reduction appears to be predominantly driven by improvement in SBP. Differences in the mode of BP ascertainment vs differences in study design, that is, use of a pragmatic vs eligibility-driven approach may account for differences in findings.[26] The current findings are noteworthy as these involve a large cohort and add to the existing small body of evidence that a reduction in BP occurs in both RHTN and non-RHTN among patients in a clinical setting. Our finding of CPAP benefit in terms of SBP are important as elevated SBP has been consistently associated with adverse implications including heart failure risk in elderly patients having a SBP as low as < 115 mm Hg.[35] Control of SBP leads to reduction in mortality, stroke, and heart failure events.[36,37] Even modest reductions in BP of 2 to 3 mm Hg can reduce coronary artery disease by 4% to 5% and stroke by 6% to 8%.[38] These effectiveness data underscore the importance of SDB management in RHTN and non-RHTN populations to improve BP to mitigate long-term adverse cardiovascular consequences.

It is interesting to note that patients with cardiac history had lower BP profiles and patients with diabetes had lower MAP and DBP. A potential explanation for this observation is that these patients may have closer follow-up and may receive more intensive medical management compared with those without cardiac comorbidity. It is recognized that isolated systolic hypertension occurs with increasing age,[39] therefore, the relatively lower diastolic and mean arterial systolic pressures observed relative to systolic pressure are anticipated.

The role of rostral neck edema in heart failure and particularly in RHTN is becoming increasingly recognized. Neck circumference has been shown to be independently associated with coexistence of HTN in SDB[40] and may represent greater rostral edema shift in RHTN compared with HTN.[19] RHTN and its association with hyperaldosteronism[41]-mediated fluid retention can potentially cause more rostral edema.

Our model revealed neck size to be a better anthropometric measure than BMI, supporting the concept that in hypertensive patients, rostral fluid displacement participates in the pathogenesis of SDB by narrowing the upper airway, thereby rendering susceptibility to a collapsed airway during sleep.

The large sample size, long follow-up duration up to 1 year and reduction in BP noted in a real-world population were some of the major strengths of our study. Limitations include the retrospective design and potential selection bias. We relied on self-reported PAP adherence data, classifying 81% of our subjects as adherent, which is comparable to other large cohorts.[42] While objective adherence data were not available for the current study, we previously reported a significant correlation between objective and self-reported adherence in patients with SDB treated in our center.[43] The dose of antihypertensive pharmacotherapy and medication adherence could not be ascertained which may have led to misattribution of true resistant hypertension in the actual setting of pseudoresistance and thereby could possibly have partially explained the lack of BP difference in terms of PAP response between the groups. Ambulatory BP measurements were not obtained, however, we have previously shown that resting BP values moderately correlate with the ambulatory BP values[44] and thus any systematic BP measurement, while affecting study data, would not have affected the generalizability of findings.

Conclusions

In conclusion, CPAP therapy reduced BP parameters in a large, clinic-based population of patients with RHTN and those who were non-RHTN by a similar extent which has important implications for clinicians managing HTN populations by providing guidance in terms of anticipated BP response from CPAP intervention in the real-world setting in patients with SDB. Future studies exploring effects of CPAP therapy on other outcomes in HTN populations are required.

Acknowledgments

Author contributions: H. K. W. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects S. D. G., D. E. M., G. T., N. F.-S., E. L. B., and R. M. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Financial/nonfinancial disclosures: R. M. has served on the CareCore National Medical Advisory Board. Her institution has received equipment and supplies from Philips Respironics/Koninklijke Philips NV for use in National Institutes of Health (NIH)-funded studies. She has received NIH funding and has received speaking honoraria from the American Academy of Sleep Medicine. N. F.-S. receives grant support from UCB, Inc, Jazz Pharmaceuticals plc, and ResMed and serves on the Speaker's Bureau for Jazz Pharmaceuticals plc. None declared (H. K. W., S. D. G., D. E. M., G. T., and E. L. B.).

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: We thank the Cleveland Clinic Knowledge Program and Optimizing Healthcare Decisions teams for the electronic health record data and Brian Wells, MD, PhD, for assistance in identifying medications for data queries. We also thank Srividya Ramachandran, PhD, for medical writing and editorial services for the manuscript from Neurological Institute, and Nicolas Thompson, MS, for additional statistical assistance.

References

1. Perkovic V, Huxley R, Wu Y, Prabhakaran D, MacMahon S. The burden of blood pressure-related disease: a neglected priority for global health. *Hypertension*. 2007;50(6):991-997.
2. Lawes CM, Vander Hoorn S, Rodgers A; International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. *Lancet*. 2008;371(9623):1513-1518.
3. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. *JAMA*. 2003;290(2):199-206.
4. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension*. 2011;57(6):1076-1080.
5. Calhoun DA, Jones D, Textor S, et al; American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008;117(25):e510-e526.
6. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation*. 2011;124(9):1046-1058.
7. Calhoun DA. Apparent and true resistant hypertension: Why not the same? *J Am Soc Hypertens*. 2013;7(6):509-511.
8. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation*. 2012;125(13):1635-1642.
9. Irvin MR, Booth JN III, Shimbo D, et al. Apparent treatment-resistant hypertension and risk for stroke, coronary heart disease, and all-cause mortality. *J Am Soc Hypertens*. 2014;8(6):405-413.
10. Thomopoulos C, Michalopoulou H, Kasiakogias A, Kefala A, Makris T. Resistant hypertension and obstructive sleep apnea: the sparring partners. *Int J Hypertens*. 2011;2011:947246.
11. Lavie L. Obstructive sleep apnoea syndrome–an oxidative stress disorder. *Sleep Med Rev*. 2003;7(1):35-51.
12. Pratt-Ubunama MN, Nishizaka MK, Boedefeld RL, Cofield SS, Harding SM, Calhoun DA. Plasma aldosterone is related to severity of obstructive sleep apnea in subjects with resistant hypertension. *Chest*. 2007;131(2):453-459.
13. Gonzaga CC, Gaddam KK, Ahmed MI, et al. Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. *J Clin Sleep Med*. 2010;6(4):363-368.
14. Pimenta E, Stowasser M, Gordon RD, et al. Increased dietary sodium is related to severity of obstructive sleep apnea in patients with resistant hypertension and hyperaldosteronism. *Chest*. 2013;143(4):978-983.
15. Foster GE, Hanly PJ, Ahmed SB, Beaudin AE, Pialoux V, Poulin MJ.

Intermittent hypoxia increases arterial blood pressure in humans through a Renin-Angiotensin system-dependent mechanism. *Hypertension*. 2010;56(3):369-377.

16. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96(4):1897-1904.
17. Parati G, Di Rienzo M, Bonsignore MR, et al. Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep. *J Hypertens*. 1997;15(12 pt 2):1621-1626.
18. Jelic S, Lederer DJ, Adams T, et al. Vascular inflammation in obesity and sleep apnea. *Circulation*. 2010;121(8):1014-1021.
19. Friedman O, Bradley TD, Logan AG. Influence of lower body positive pressure on upper airway cross-sectional area in drug-resistant hypertension. *Hypertension*. 2013;61(1):240-245.
20. Montesi SB, Edwards BA, Malhotra A, Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Clin Sleep Med*. 2012;8(5):587-596.
21. Schein AS, Kerkhoff AC, Coronel CC, Plentz RD, Sbruzzi G. Continuous positive airway pressure reduces blood pressure in patients with obstructive sleep apnea; a systematic review and meta-analysis with 1000 patients. *J Hypertens*. 2014;32(9):1762-1773.
22. Lozano L, Tovar JL, Sampol G, et al. Continuous positive airway pressure treatment in sleep apnea patients with resistant hypertension: a randomized, controlled trial. *J Hypertens*. 2010;28(10):2161-2168.
23. Muxfeldt ES, Margallo V, Costa LM, et al. 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. *Hypertension*. 2015;65(4):736-742.
24. Pedrosa RP, Drager LF, de Paula LK, Amaro AC, Bortolotto LA, Lorenzi-Filho G. Effects of OSA treatment on BP in patients with resistant hypertension: a randomized trial. *Chest*. 2013;144(5):1487-1494.
25. Iftikhar IH, Valentine CW, Bittencourt LR, et al. Effects of continuous positive airway pressure on blood pressure in patients with resistant hypertension and obstructive sleep apnea: a meta-analysis. *J Hypertens*. 2014;32(12):2341-2350, discussion 2350.
26. Martínez-García MA, Capote F, Campos-Rodríguez F, et al; Spanish Sleep Network. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA*. 2013;310(22):2407-2415.
27. Varounis C, Katsi V, Kallikazaros IE, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: a systematic review and meta-analysis. *Int J Cardiol*. 2014;175(1):195-198.
28. Dernaika TA, Kinasewitz GT, Tawk MM. Effects of nocturnal continuous positive airway pressure therapy in patients with resistant hypertension and obstructive sleep apnea. *J Clin Sleep Med*. 2009;5(2):103-107.
29. Iber C, Ancoli-Israel S, Chesson AL Jr, Quan SF; American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
30. Katzan I, Speck M, Dopler C, et al. The Knowledge Program: an innovative, comprehensive electronic data capture system and warehouse. *AMIA Annu Symp Proc*. 2011;2011:683-692.
31. Billings ME, Kapur VK. Medicare long-term CPAP coverage policy: a cost-utility analysis. *J Clin Sleep Med*. 2013;9(10):1023-1029.
32. Davies RJ, Ali NJ, Stradling JR. Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome. *Thorax*. 1992;47(2):101-105.
33. Burnham KP, Anderson DR. *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach*. 2nd ed. New York, NY: Springer-Verlag; 2002.
34. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2014.
35. Butler J, Kalogeropoulos AP, Georgiopoulou VV, et al. Systolic blood pressure and incident heart failure in the elderly. The Cardiovascular Health Study and the Health, Ageing and Body Composition Study. *Heart*. 2011;97(16):1304-1311.
36. Staessen JA, Thijs L, Fagard R, et al; Systolic Hypertension in Europe Trial Investigators. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA*. 1999;282(6):539-546.
37. Kostis JB, Davis BR, Cutler J, et al; SHEP Cooperative Research Group. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA*. 1997;278(3):212-216.
38. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252.
39. Aronow WS, Fleg JL, Pepine CJ, et al; ACCF Task Force. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation*. 2011;123(21):2434-2506.
40. Min HJ, Park AY, Kim da H, Lee JG, Park S, Cho HJ. Neck circumference and lowest oxygen saturation are independently associated with high coexistence of hypertension in obstructive sleep apnea. *Yonsei Med J*. 2014;55(5):1310-1317.
41. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension*. 2002;40(6):892-896.
42. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc*. 2008;5(2):173-178.
43. Su CS, Liu KT, Panjapornpon K, Andrews N, Foldvary-Schaefer N. Functional outcomes in patients with REM-related obstructive sleep apnea treated with positive airway pressure therapy. *J Clin Sleep Med*. 2012;8(3):243-247.
44. Walia HK, Li H, Rueschman M, et al. Association of severe obstructive sleep apnea and elevated blood pressure despite antihypertensive medication use. *J Clin Sleep Med*. 2014;10(8):835-843.