European Review for Medical and Pharmacological Sciences 2019; 23: 9612-9624

Resistant hypertension and obstructive sleep apnea syndrome in therapy with continuous positive airway pressure: evaluation of blood pressure, cardiovascular risk markers and exercise tolerance

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Abstract. – OBJECTIVE: Resistant hypertension (RH) may be associated with Obstructive Sleep Apnea (OSA), determining a remarkable increase in cardiovascular risk. The aim of the study was to assess the effect of six months with continuous positive airway pressure (CPAP) treatment on blood pressure (BP) values, cardiovascular risk markers, and exercise tolerance in patients with RH and OSA.

PATIENTS AND METHODS: Twenty-four patients with RH and OSA were recruited and 24-hour ambulatory BP, intima-media thickness (IMT), flow mediated dilation (FMD), renal resistive index (RRI), and endurance cardiopulmonary exercise testing (CPET) were obtained at enrollment and after 6-month treatment.

RESULTS: Significant reduction in clinic systolic and diastolic BP, IMT, and RRI ($p = 0.003$, $p = 0.009$, $p = 0.020$, $p = 0.04$, respectively) and increase in the left ventricular ejection fraction ($p = 0.035$) were observed after a 6-month therapy with CPAP. Moreover, improvement in all polysomnographic parameters (number of apneas/hypopneas per hour ($p < 0.001$), number of episodes of night-time hemoglobin desaturation (ODI) ($p = 0.010$)), an improvement in Epworth Sleepiness Scale ($p < 0.001$), as well as in endurance time during constant workload CPET ($p = 0.017$) were observed too.

CONCLUSIONS: CPAP treatment for six months reduces BP and improves cardiovascular risk and exercise tolerance in patients with RH and OSA. An extended cardiovascular assessment, including exercise testing, might be helpful in this population, given the possible reversibility of some endothelial dysfunction and atherosclerotic markers with CPAP treatment, as reported in our study.

Key Words:
Obstructive sleep apnea syndrome, Continuous positive airways pressure treatment, Resistant hypertension, Exercise tolerance, Intima media thickness, Flow mediated dilation, Renal resistive index.

Introduction

Obstructive Sleep Apnea (OSA) is a sleep disorder characterized by total (apnea) or reduced (hypopnea) cessation of airflow caused by repeated episodes of total or partial upper airway obstruction, respectively, with subsequent recovery of regular breathing after respiratory efforts resulting in awakening[1]. According to the International Classification of Sleep Disorders, OSA is defined by the presence of snoring, daytime sleepiness, non-restorative sleep, morning headache, asthenia, awakening with choking sensation, and alteration of performances together with at least 5 obstructive respiratory events (i.e., apneas, hypopneas or respiratory effort-related arousals) for hour of sleep. Moreover, the presence of ≥ 15 obstructive respiratory events per hour of sleep, in the absence of sleep-related symptoms, is also sufficient to diagnose OSA[2,3]. The prevalence of OSA in the general adult population is about 14% in males and 7% in women, although it still remains a frequently misdiagnosed disease[3]. Respiratory sleep disorders are of great socio and economic relevance and represent a known risk factor of cardiovascular

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and renal diseases[4]. These disorders are associated with the development of arterial hypertension and abnormalities in the physiological circadian variation of blood pressure (BP) control. Scholars[5] have shown that moderate and severe OSA is an independent cause of arterial hypertension and that these subjects have a 3.2-fold higher risk of developing hypertension compared to healthy individuals. Furthermore, OSA is one of the main causes of secondary resistant hypertension (RH) with an extremely high prevalence, equal to 70-83% in this population[6]. "Resistant" (or "refractory") hypertension is defined when the recommended BP goals cannot be achieved in the presence of lifestyle changes and combination therapy with at least three different classes of anti-hypertensive drugs, including a diuretic, taken at the maximum recommended or tolerated dose[7]. The mechanisms leading to vascular damage in OSA are not well known, but it is assumed that the cycles of intermittent hypoxia caused by nocturnal respiratory events lead to altered chemoceptorial and baroceptorial activity, hyperactivation of the sympathetic nervous system, endothelial dysfunction mediated by vasoactive substances, and systemic inflammation with an increase in peripheral resistances and, consequently, in BP[8]. Continuous positive airway pressure (CPAP) is the gold standard therapy for preventing airway collapse, with demonstrated improvement in symptoms and reduction of cardiovascular and renal risks[9,10]. Multiple studies[11,12] have shown discordant data about the impact of CPAP therapy on BP. This impact should be greater in RH, but even this aspect is not completely understood. Some authors have shown that among patients with RH and OSA, treatment with CPAP for three months leads to a reduction in BP values within 24 hours. Of note, this effect was seen in patients with 24-hour ambulatory BP monitoring (ABPM)-confirmed RH, who use CPAP more than 5.8 hours[13]. Sleep respiratory disorders, as well as having an impact on endothelium, promoting cardiovascular and renal damage, have been shown to affect physical activity, causing impaired ventilatory response to exercise that improves after CPAP therapy[14,15]. At present, knowledge about the impact of sleep breathing disorders on exercise capacity is controversial, as the latter could be also influenced by body mass index (BMI) and fat mass. Indeed, Rizzi et al[16] have shown that lean patients with OSA do not suffer from functional limitations during exertion, whereas decreased tolerance to cardiopulmonary exercise testing (CPET) has been demonstrated in obese subjects. Moreover, Mirrakhimov[17] hypothesized that the hypervolemic condition associated with OSA could be associated with a decrease in exercise tolerance. Nonetheless, no data are available concerning the physiological response to exercise and the effects of CPAP among patients suffering from RH secondary to OSA. The aim of the present study was to longitudinally assess the effects of a six-month long treatment with CPAP on BP values, markers of endothelial damage and atherosclerosis, echocardiographic parameters, and exercise tolerance in patients with OSA-related RH.

Patients and Methods

Patients

Twenty-four patients suffering from RH referred to the Hypertension Center – Nephrology Unit of the Department of Translational and Precision Medicine of "Policlinico Umberto I" Hospital/"Sapienza" University of Rome, Italy, were recruited in a prospective longitudinal study. Diagnosis of RH was made according to the last guidelines by the European Society of Hypertension/European Society of Cardiology Task Force[18].

The study protocol was approved by the Local Ethics Committee and the study has been conducted in agreement with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained for each enrolled participant.

Patients with other known causes of secondary hypertension (renal artery stenosis, primary and secondary hyperaldosteronism, pheochromocytoma, Cushing syndrome, parathyroid disorders, coarctation of the aorta) were excluded from the study, as well as those with comorbidities, such as malignancies, acute cardiovascular, and cerebrovascular diseases, chronic heart failure (NYHA class III-IV) or acute heart failure, anemia, respiratory disorders (chronic obstructive pulmonary disease, asthma, interstitial lung diseases, chronic respiratory failure on long-term oxygen therapy), neuromuscular diseases, moderate renal impairment (estimated glomerular filtration rate < 59 mL/min). Ongoing treatment with psychotropic drugs affecting ventilatory drive, pregnancy, and inability to perform exercise testing on a cycle ergometer were part of the exclusion criteria too. All participants underwent the following procedures at the time of enrollment (t0) and after a 6-month treatment with CPAP (t1): clinical measurement of resting BP, 24-hour ABPM, home-based cardiorespiratory sleep study, ultrasound

assessment of carotid intima-media thickness (IMT), flow-mediated dilation (FMD) and renal resistive index (RRI), echocardiography, spirometry and CPET.

Blood Pressure Measurements

Blood pressure measurements were made in the dominant arm, after 10 minutes of rest in the sitting position, using a standard automatic sphygmomanometer and cuffs adapted to the arm circumference[19]. The mean of the three different measurements was recorded and used for statistical analyses. The systolic BP (SBP) and diastolic BP (DBP) were taken as the points of appearance and disappearance of Korotkoff sounds, respectively. Arterial hypertension was defined as SBP ≥140 mmHg and/or DBP ≥ 90 mmHg on repeated measurements.

24-Hour Ambulatory Pressure Monitoring

A 24-hour ABPM was performed to estimate the mean total and daytime SBP and DBP values. BP measurements were obtained at regular intervals of 15 minutes during the daytime period and 30 minutes at night, through a specific device (ABP Spacelabs Healthcare, Snoqualmie, WA, USA) using a cuff applied to the upper left limb. Patients were instructed to perform normal daily activities except for too intense physical exercise during monitoring and, at the time of inflation, not to move and to keep the arm at level of the heart. In a dedicated diary, patients were requested to report information on disturbances or events that could influence the measurements. Furthermore, the time of medications administration, meals, and the period of sleep was also indicated. Recorded data[20] were analyzed according to the recommendations of the European Society of Hypertension. The study was considered valid if ≥ 70% of the measurements were present, both for daytime and nighttime. BP average values < 130/80 mmHg in the 24 hours, < 135/85 mmHg during the daytime and in the waking period and < 120/70 mmHg during the nighttime were considered normal. The night/day ratio of nighttime and daytime mean pressures was evaluated to verify the presence of the dipping effect, represented by the physiological night pressure drop > 10% with respect to the diurnal value.

Home-Based Cardiorespiratory Sleep Study

A home-based cardiorespiratory sleep study was performed by using a SOMNO Screen Plus device (SOMNOmedics GmbH, Randersacker, Germany), which allowed to monitor chest and abdominal movements, nasal flow, body position, oxygen saturation, snoring, and heart rate (HR). Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) and symptoms, such as daytime sleepiness, non-restorative sleep, fatigue, insomnia, snoring, witnessed breathing interruptions, morning headaches, recurrent awakenings, due to gasping or choking were recorded. Analysis of data[21] was performed according to the American Academy of Sleep Medicine 2007 guidelines. Apnea was defined as the cessation of airflow ≥ 10 seconds (s), whilst hypopnea was defined either as an airflow reduction of ≥ 30% from baseline associated with a fall in oxygen saturation (SpO_2) ≥ 4% or as an airflow reduction of ≥ 50% from baseline with a fall in SpO_2 ≥ 3% for 10 s or more. Number of apneas and hypopneas per hour (apnea/hypopnea index, AHI), percentage of total sleep time spent with an SpO_2 lower than 90% (T90), and the number of oxygen desaturations per hour (oxygen desaturation index, ODI) were extrapolated for each patient. Diagnostic criteria for OSA were AHI ≥ 5 in symptomatic patients or AHI ≥ 15 in the absence of sleep-related symptoms.

Continuous Positive Airway Pressure

The optimal CPAP level for each patient was determined by titration with auto-CPAP device iSleep 20 (MedicAir, Pogliano Milanese, Italy) during four consequent nights, using pressures between 4 and 20 cm/H_2O. Compliance to ventilation therapy was defined as an average use of CPAP ≥ 4 hours per night. OSA treatment was considered effective if the patient was compliant, and the AHI was reduced by ≥ 50% from baseline or below 10 events/hour.

Carotid Intima-Media Thickness Assessment

Right (R) and left (L) carotid ultrasound was blindly performed by an experienced sonographer, who was unaware of the characteristics of the patients under examination. The participants were studied with the high-resolution B-mode ultrasound machine Toshiba Aplio XV (Toshiba Aplio XV, Toshiba American Medical Systems, Inc, Tustin, CA, USA) equipped with a 5-MHz to 12-MHz linear transducer with a 0.01-mm resolution, following a standardized vascular protocol[22]. The same equipment was used for the assessment of brachial artery FMD (see below). IMT was measured at three points on the far walls of both left and right distal common carotid arteries, ca-

rotid bulb, and the proximal portion of the internal carotid arteries. The mean IMT was calculated as the average IMT on both sides. The value of IMT was considered normal when between 0.55 and 0.9 mm[23].

Brachial Artery Flow-Mediated Dilation

According to the method described by Patel et al[24] the endothelium-dependent vasodilation of the brachial artery was assessed by the same blinded experienced ultrasonographer, following a standardized vascular protocol[25]. FMD was defined by the change in post-stimulus arterial diameter, expressed as a percentage of baseline diameter, as follows: FMD = [(post-hyperemia diameter – basal diameter)/ basal diameter] x 100.

FMD was considered normal if higher than 10%.

Renal Resistive index

Participants were studied with the high-resolution B-mode ultrasound machine Toshiba Aplio XV (Toshiba Aplio XV, Toshiba American Medical Systems, Inc, Tustin, CA, USA) equipped with a 3-3.5 MHz convex transducer. All measurements were made by a single, blinded, experienced ultrasonographer. RRI values were registered as the mean of three separate measurements in the renal superior pole, interpolar region, and inferior pole at the level of the interlobular, interlobar or arcuate arteries for both kidneys. We used an anterior and an oblique approach, to detect the renal arteries and intra-parenchymal vessels. Three to five reproducible and consecutive waveforms with similar aspect from each kidney were obtained. These measurements were used to calculate the average RRI value for each kidney, then, the average RRI value for each patient was calculated as the mean of left and right kidney RRI[26]. Peak systolic velocity and end-diastolic velocity (centimeters/second) were determined to calculate the RRI as follows: RRI = [1 – (end-diastolic velocity/ peak systolic velocity)] x 100.

Echocardiography

All patients underwent transthoracic echocardiography with a commercially available cardiovascular ultrasound system (Vivid E9, GE Healthcare, Little Chalfont, Buckinghamshire, UK). Measurements of cardiac chambers were made according to the established criteria[27,28.] Left Ventricular ejection fraction (LVEF) by modified biplane Simpson method and mass index were estimated. Peak early (E) and late (A) diastolic velocities, deceleration time, left ventricular isovolumic relaxation time, and myocardial performance index were obtained using standard Doppler practices. Standard parasternal, apical, and subcostal views were used.

Pulmonary Function Testing

Spirometry was performed with the subject in the sitting position, according to international recommendations[29,30]. Flow-meter calibration was repeated before each testing using a certified 3-liters syringe. An automated lung function testing system (Quark PFT, COSMED, Rome, Italy) was used to measure dynamic lung volumes (i.e., forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)). The volumes are expressed as raw values and percentage of predicted.

Cardiopulmonary Exercise Testing

Incremental symptom-limited exercise testing was performed for every participant on an electronically braked cycle ergometer through automated testing system (OMNIA, COSMED, Rome, Italy), in accordance with international recommendations[31].

Incremental protocol consisted of a steady state resting period, then, one minute of warm-up with no load followed by a stepwise protocol in which the work rate was increased by 10 Watts per minute. The test was considered maximal for respiratory exchange ratio (RER) values > 1.05. Testing was continued until the point of symptom limitation (i.e., peak exercise). Subjects were asked to score their sense of breathlessness and muscle fatigue throughout the exercise and at peak exercise using the modified 10-point Borg scale[32]. All participants were continuously monitored by means of a 12-lead electrocardiograph. BP was measured every minute using a sphygmomanometer. Oxygen consumption ($V'O_2$), carbon dioxide output ($V'CO_2$), tidal volume (VT), respiratory frequency, and minute ventilation (V'E) were analyzed breath-by-breathe during the test. SpO_2 was continuously monitored. All measured and derived parameters [e.g., ventilatory equivalents for O_2 and CO_2 ($V'E/V'O_2$) and $V'E/V'CO_2$, respectively, end tidal O_2, and CO_2 partial pressures ($PETO_2$ and $PETCO_2$, respectively)] were recorded and averaged every fifteen seconds. Lactate threshold (LT) was non-invasively determined by the use of the dual methods approach (V-slope and ventilatory equivalents methods)[33]. $V'O_2$ at peak exercise ($V'O_2$ peak) was normalized for body weight and also expressed as percentage of predicted value. Furthermore, after two hours, ev-

Table I. Baseline characteristics of population study. The values are presented as mean ± standard deviation or proportions, except for time spent with SaO_2 < 90% which is presented as median (*range*).

Characteristics	Patients with OSAS and RH (n=12)
Age (y)	60.3 ± 9.9
Sex M/F (n/%)	12 (100)/0 (0)
BMI	29.6 ± 3.4
Neck circumference (cm)	43.1 ± 2.4
Epworth Sleepiness Scale	9.9 ± 4.6
Mallampati score	3.1 ± 0.5
Years since diagnosis of resistant hypertension	12.9 ± 7.1
Ex-smokers (yes/no)	3/9
Diabetes mellitus (n/%)	7 (58.3)
Past cardiovascular events (n/%)	3 (25)
Numbers antihypertensive drugs	3.7 ± 0.9
Diuretics (%)	100
ACE inhibitor (%)	50
AR-blockers (%)	50
β-blockers (%)	50
Calcium channel blockers (%)	66
Direct vasodilators (%)	33
Central alpha agonists (%)	25
AHI (event/hour)	28.7 ± 12.2
TSat 90, median % (range)	19.6 (3.6 – 35.5)
Mean O_2 saturation, %	92.3 ± 2.0
ODI (event/hour)	34.7 ± 16.5
Clinical blood pressure (mmHg)	
SBP	145.5 ± 17.6
DBP	84.2 ± 12.4
24-h SBP (mm Hg)	143.4 ± 15.1
Diurnal	139.1 ± 13.8
Nocturnal	129.8 ± 20.3
24-h DBP (mm Hg)	85.5 ± 8.2
Diurnal	82.9 ± 6.6
Nocturnal	77.9 ± 10.1
Nondipping pattern (n/%)	8 (66.6)

Abbreviations: BMI, body mass index; AHI, apnea-hypopnea index; TSat 90, time with oxygen arterial saturation < 90%; ODI, oxygen desaturation index; SBP, systolic blood pressure; DBP, diastolic blood pressure; 24-h SBP, 24-hour mean systolic blood pressure; 24-h DBP, 24-hour mean diastolic blood pressure.

ery patient performed a second constant workload sub-maximal endurance test. Workload was set at 80% of the maximal workload tolerated during the symptom-limited test. Time to exhaustion (Tlim) was registered and used for analysis. All CPETs were performed and analyzed by two doctors with long-standing expertise in the field of exercise testing, blinded to the characteristics of the patients.

Statistical Analysis

Distribution of continuous data was assessed with the Shapiro-Wilk test. Normally and non-normally distributed data are expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), respectively. Student's *t*-test for paired data and Wilcoxon signed-rank test were used to test the changes in the registered parameters from t0 to t1, according to Gaussian or non-Gaussian data distribution, respectively. χ^2 analysis tested the association between categorical variables. Bivariate correlations were identified with Pearson's and Spearman's rank tests, for normally and non-normally distributed data, respectively. A p-value < 0.05 was considered as statistically significant. Analysis was performed using the Statistical Product and Software Solution (SPSS) Statistics version 22.0 software package (IBM Corp., Armonk, NY, USA).

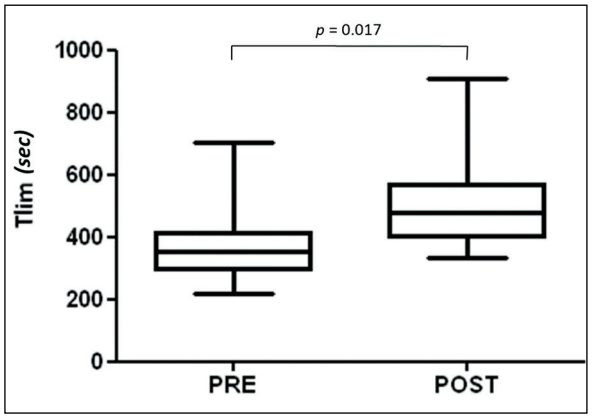

Figure 1. Variation of limit of tolerance (Tlim, expressed as exercise time in seconds) during endurance CPET at constant load, before and after CPAP (Tlim 508.4 ± 153.5 sec *vs.* Tlim baseline 372.3 ± 121.7 sec, $p = 0.017$).

Results

Twenty-four consecutive patients (20 males) affected by RH were recruited for the study, with a mean age of 60.3 ± 9.9 years, mean BMI of 28.7 ± 3.3 kg/m² and an average illness duration of nearly 13 years. OSA was detected in 22/24 cases (91.6%), with an average AHI of 22.6 ± 16.3 events/hour. Ten out of twenty-two patients dropped out due to refusal to start with proposed CPAP treatment; the remaining twelve patients completed the study with full re-assessment at t1.

Baseline characteristics of the study population are shown in Table I. Clinic SBP and DBP were 145.0 ± 17.6 and 84.2 ± 12.4 mmHg, respectively, whilst mean baseline 24-hour SBP and DBP were 143.4 ± 15.2 mmHg and 85.5 ± 8.2 mmHg, respectively. Non-dipper BP nocturnal pattern was observed in 8 (66%) cases. The study group

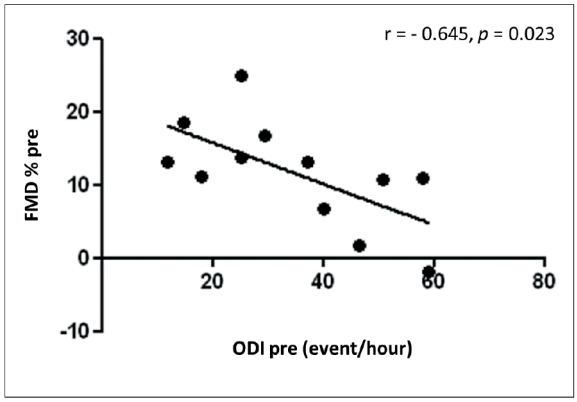

Figure 2. Correlation between baseline flow mediated dilation (FMD %) and pre-CPAP oxygen desaturation index (ODI) (r = -0.645, $p = 0.023$).

received anti-hypertensive therapy unchanged for at least two weeks prior to the study and maintained it for its whole duration. Anti-hypertensive medications consisted of diuretics in all patients, calcium-channel blockers in 8 cases, β-adrenergic receptor blockers in 6 cases, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers (ARBs) in 6 cases and drugs with central and α-chemical action in 3 and 4 subjects, respectively.

Mean baseline AHI was 28.7 ± 12.2 events/hour, 50% of patients had a severe OSA and the others were diagnosed with mild-to-moderate OSA. Average ESS was 9.9 ± 4.6. Mean use of CPAP was 6.4 ± 1.3 hours per night and mean CPAP pressure used was 8.2 ± 0.4 cmH_2O. Adequate control of sleep-related respiratory events was recorded at t1, with residual AHI of 3.4 ± 3.8 events/hour ($p < 0.001$), compared to baseline, number of episodes of night-time hemoglobin desaturation (ODI) ($p = 0.010$), and ESS of 4.7 ± 1.9 ($p < 0.001$). A statistically significant reduction in clinic SBP ($p = 0.003$) and DBP ($p = 0.009$) was found after 6 months with CPAP (Table II). Significant reduction in ABPM values was also found for mean 24-hour SBP (nearly 16 mmHg, $p = 0.007$) and 24-hour DBP (approximately 7 mmHg, $p = 0.021$). Sub-analysis of ABPM daily phases showed significant changes in the mean daytime SBP and nighttime DBP (Table II). No modifications, instead, were observed with regards to nighttime dipping pattern. Ultrasound assessment showed significant reduction in IMT ($p = 0.020$) and RRI ($p = 0.036$) at t1 compared to baseline (Table III), whilst brachial artery FMD did not change significantly with CPAP treatment. At echocardiography, LVEF only improved after ventilatory therapy ($p = 0.03$), with no significant changes among the other cardiac indices (Table III). Moreover, no differences were found in terms of exercise tolerance and physiological responses to exercise at incremental workload CPET at t1. However, endurance time (i.e., Tlim) at constant workload CPET showed a significant increase ($p = 0.017$) (Figure 1). FMD at baseline was negatively related with ODI (r = 0.65, $p = 0.023$) (Figure 2). Negative correlations were also observed between 24-hour mean SBP and Tlim (r = -0.76, $p = 0.004$) and between 24-hour mean DBP and Tlim (r = -0.83, $p = 0.001$) at the beginning of the study (Figure 3).

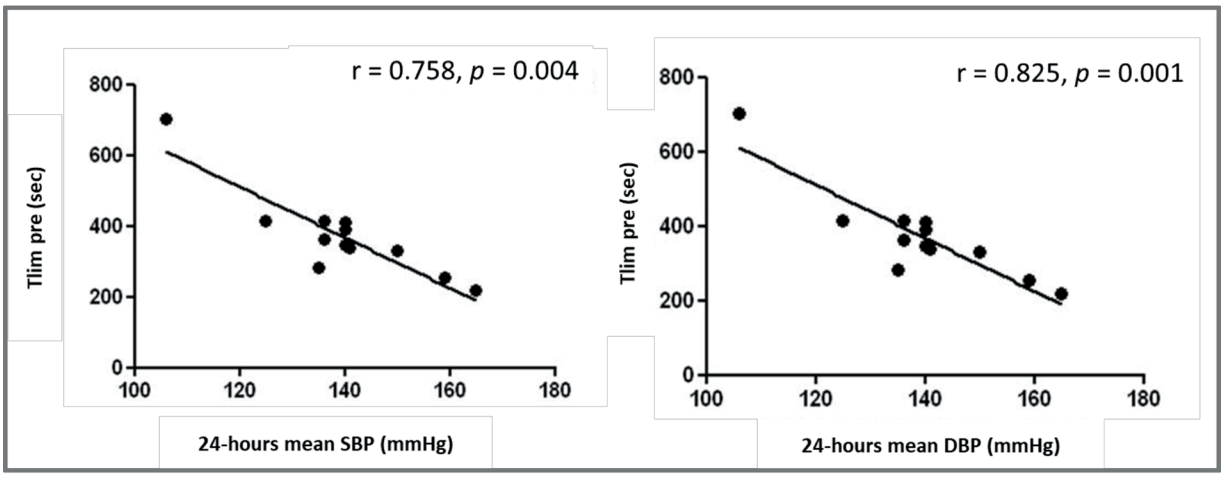

Figure 3. Correlation between baseline 24-hour mean systolic blood pressure (SBP) and limit of tolerance pre-CPAP (Tlim pre, expressed as exercise time in seconds) (r = -0.758, $p = 0.004$) and between 24-hour mean diastolic blood pressure (DBP) and Tlim pre (r = -0.825, $p = 0.001$).

Table II. Effect of 6-month continuous positive airway pressure treatment on blood pressure levels. Values are presented as mean ± standard deviation or proportions. Abbreviations: BP, blood pressure.

	Baseline	CPAP (6 months)	*p*-value
Systolic BPs (mmHg)			
Clinic	145.5 ± 17.6	127.9 ± 11.63	0.00
24 hours	143.4 ± 15.1	127.8 ± 10.2	0.01
Daytime	139.1 ± 13.8	129.1 ± 9.9	0.01
Night-time	129.8 ± 20.3	122.3 ± 14.1	n.s.
Diastolic BPs (mmHg)			
Clinic	84.2 ± 12.4	72.5 ± 7.8	0.01
24 hours	85.5 ± 8.2	78.3 ± 4.8	0.02
Daytime	82.9 ± 6.6	79.9 ± 4.8	n.s.
Night-time	77.9 ± 10.1	72.5 ± 7.8	0.02
Nocturnal blood pressure pattern (n/%)			
Dipper	8 (66.6)	8 (66.6)	n.s.
Nondipper	4 (33.4)	4 (33.4)	n.s.

Table III. Effect of 6-month CPAP treatment on cardiovascular markers of the study group. Values are presented as mean ± standard deviation or proportions. Abbreviations: IMT, intima media thickness; RRI, renal resistive index; FMD %, flow mediated dilation %; LVEF, left ventricle ejection fraction; LVM index, left ventricular mass; PAPs, pulmonary artery systolic pressures.

Variable	Baseline	CPAP (6 months)	*p*-value
IMT	1.3 ± 0.3	1.0 ± 1.2	0.02
RRI	0.7 ± 0.7	0.6 ± 0.1	0.04
FMD (%)	9.9 ± 8.9	9.8 ± 8.4	n.s.
LVEF (%)	55.9 ± 4.1	59.9 ± 4.3	0.03
LVM index (g/m^2)	127.9 ± 22.5	126.3 ± 19.2	n.s.
Posterior wall (cm)	1.1 ± 0.1	1.1 ± 0.2	n.s.
Interventricular septum (cm)	1.2 ± 0.1	1.1 ± 0.2	n.s.
Diastolic dysfunction, n (%)	6 (50%)	3 (25%)	n.s.
PAPs (mmHg)	29.78± 3.7	28.7 ± 8.9	n.s.

Discussion

Increasing reports in literature show that OSA is associated with higher cardiovascular and renal morbidity and that OSA represents an independent risk factor for the development of arterial hypertension[4,6]. Recurrent cycles of intermittent hypoxia stemming from obstructive respiratory events cause chemoceptorial and baroceptorial hypersensitivity, with subsequent sympathetic nervous system hyperactivation, which, together with endothelial dysfunction and systemic inflammation, leads to the activation of peripheral vasoconstriction and impaired vasodilatation[34,35]. Logan et al[36] have shown that sleep respiratory disorders contribute to poor control of systemic hypertension, especially in patients with RH. According to previous investigations, we have confirmed a high prevalence of OSA in our study group affected by RH[6]. A great variability has been observed with regards to the effects of treatment with CPAP on BP, probably as a result of the multifactorial nature of systemic hypertension[37,38]. Despite conflicting data, different meta-analyses showed agreement on a mild CPAP-induced reduction in SBP and DBP values, with an approximate fall of 2 mmHg. The impact of ventilation therapy should be more evident in patients with RH[12,39]. Not many studies have assessed before the role of CPAP treatment in patients with RH and OSA. The HIPARCO trial[40] showed that CPAP treatment for 12 weeks results in a decrease in 24-hour mean SBP and DBP and an improvement in the nocturnal pressure pattern. However, these results may be affected by the fact that the chosen treatment interval with CPAP was too

short to eventually observe larger improvements in clinical outcomes. Indeed, Dernaika et al[41] in a previous retrospective observational study suggested that the full beneficial effects of ventilation may only be observed after 6 months of treatment. One single six-month study[42] showed that CPAP treatment does not have a significant effect on clinical and ambulatory BP in patients with RH and moderate-to-severe OSA, although beneficial effects on nighttime SBP and on nocturnal BP fall might exist in patients with uncontrolled ambulatory BP levels[43]. On the contrary, in our study group a large reduction in clinic SBP and DBP and in 24-hour mean systolic and diastolic values was observed, after a six-month long follow-up. Analyzing the different phases of the day, it was found that the decrease was actually observed for SBP during daytime and for DBP during the night. It has been consistently demonstrated[44,45] that nighttime SBP is a better cardiovascular risk predictor than daytime or clinic BP values, both in general hypertensives and in patients with RH. However, controlling SBP remains more difficult. Moreover, Evequoz et al[46] demonstrated a tendency toward a reduced nocturnal BP drop with increasing apnea severity. In OSA patients with RH, conversion from non-dipping to dipping pattern secondary to CPAP treatment has been described[35,36]. This difference cannot be attributed to CPAP treatment duration. Indeed, Lozano et al[13] and Martínez-García et al[40] showed a significant restoration of dipping behavior after 12 weeks of ventilation therapy, while other authors did not report significant changes in circadian BP behavior even after more extended follow-up (24 weeks)[47]. In our research, we did not observe reversibility of dipping pattern, despite adequate adherence to therapy (i.e., greater than 6 hours per night) and the demonstration of a very good control of AHI with CPAP. The length of hypertensive disease (i.e., > 10 years) with consequent non-reversible vascular alterations and eventually the small sample size might be responsible for the discordance observed with the above-mentioned studies with regards to nocturnal dipping. Also, we did not find a relationship between the number of hours spent on CPAP therapy and the reduction in the average daily BP values. Thus, it is plausible that the absence of nocturnal SBP reduction and the unchanged non-dipping pattern may be translated into higher long-term cardiovascular risk in our study group. To our knowledge, this is the first study to evaluate the responses of cardiovascular risk markers and endothelial damage, such as IMT, FMD, and RRI, to CPAP treatment among patients with RH and OSA. Repeating cycles of hypoxemia and re-oxygenation are known to cause oxidative stress, inflammation, and activation of coagulation with impaired vascular endothelial function[48,49]. Earlier signs of atherosclerosis, such as increased IMT, may be present in the population with obstructive airway events[50]. Furthermore, severe OSA and hypertension are associated with increased arterial stiffness, but CPAP treatment appears to play a role in reducing vessel stiffness, avoiding the progression of vascular changes[51]. Scholars[52,53] have shown that long-term CPAP therapy reduces the IMT. Accordingly, in our study there was a modest but significant reduction in IMT after six months of ventilation treatment. Evidence from literature suggests that subjects with OSA have higher serum levels of vasoactive mediators, such as endothelin, and low levels of nitric oxide endothelial synthase that would lead to lower FMD of the vessels. Appropriate CPAP treatment seems to improve FMD, with potential benefits in lowering cardiovascular and renal risk[54,55]. In our study group, evidence was found of endothelial dysfunction at baseline, as represented by low mean FMD. Nonetheless, we did not observe significant changes in FMD after proper treatment with CPAP. Kraiczi et al[56] demonstrated that a low value of FMD can be related with patient's age and AHI. In agreement with those data, we observed a link between OSA severity and endothelial dysfunction, as underlined by the relationship found between higher ODI values and lower changes in FMD at baseline. At present, the role of endothelial dysfunction in the development of RH is not entirely clear[54], but we can reasonably speculate that the vascular remodeling induced by OSA might lead to a further rise in BP in subjects with arterial hypertension. Previously, Viazzi et al[26] have demonstrated that RRI is a marker of parenchymal renal damage and a predictor of renal dysfunction progression, particularly in RH. High RRI is known in patients with mild-to-moderate OSA, as well as the existence of a linear relation between AHI and RRI. This correlation seems to be independent from the concurrence of hypertension, diabetes mellitus, and advanced age. Indeed, apnea events trigger renin-angiotensin-aldosterone and sympathetic nervous systems' activation, determining a progressive structural renal damage with increased RRI and hypertension. Wissing et al[57] assessed how RRI significantly decreased among patients with OSA after

ventilation therapy, compared to those without treatment. Accordingly, we have shown that CPAP therapy causes a significant reduction in RRI too. An increased risk of multi-organ damage, together with a higher prevalence of ventricular hypertrophy are common in patients with RH, compared to those with controlled hypertension[50]. Furthermore, intermittent hypoxia, sympathetic nervous system's activation, and changes in intrathoracic pressure, due to apnea are a powerful stimulus to cardiac muscle hypertrophy, due to the differences between intra-cardiac and extra-cardiac pressure and the increased ventricle wall stress[4]. In fact, in the RESIST-POL study it is reported that concentric hypertrophy and systolic dysfunction in RH are independently associated with moderate-to-severe OSA, as well as nighttime BP levels[58]. In line with these data, we found an increased mass of the left ventricle. Moreover, no significant changes were observed with CPAP. We do hypothesize that six months only might not be sufficient to reverse the cardiac structural changes established in the long time of uncontrolled hypertensive disease, even if no significant correlations were found in our study group between ventricular hypertrophy and duration of hypertension, baseline BP values, and OSA severity. From a functional perspective, OSA is known to determine an increased left ventricle pre-load and post-load, due to the higher venous return to the heart and to the rise in cardiac transmural pressure secondary to the repetitive decreases in intrathoracic negative pressure[59]. Akar Bayram et al[60] described the positive effect of CPAP on LVEF in patients with heart failure, whilst no data are available from patients with OSA-related RH. In the present study, a significant improvement in LVEF was observed after six months of CPAP therapy. We do believe that this can be due both to the reduction in the intrathoracic pressures and to a better control of arterial BP obtained with ventilation. Finally, the changes in exercise tolerance secondary to CPAP treatment were also investigated. Mirrakhimov hypothesized that hypervolemic conditions with accumulation of body fluids, usually coexistent and correlated with the severity of apneas (e.g., heart failure and RH), could be independently associated with reduced exercise tolerance[17]. Reduced work capacity has been described in systemic hypertension compared to the healthy population with same age and level of physical training. In fact, patients with essential hypertension typically show lower cardiac output during exercise, anticipated anaerobic threshold and reduced maximal oxygen uptake[61]. Pendharkar et al[62] have shown that exercise time during CPET improves already after just one month of ventilation therapy in normotensive subjects with sleep disorders. No data are available from literature regarding exercise tolerance among patients suffering from both RH and OSA. To our knowledge, the present study is the first to assess exercise tolerance in this specific population and, moreover, to investigate on the effects of CPAP on CPET parameters. As expected, we did not find an improvement in exercise tolerance, expressed as $V'O_2$ peak measured during incremental workload CPET. However, as already demonstrated by several studies, $V'O_2$ peak is poorly sensitive in detecting the effect of a therapeutic intervention on exercise response, whilst endurance time measured during constant workload exercise testing provides a significantly higher sensitivity. Indeed, differently from $V'O_2$ peak, an average increase of more than two minutes in Tlim was observed after six months of CPAP therapy. Our study is the first one to show the positive effects of CPAP treatment on exercise tolerance among people with RH and OSA. We also considered the presence of an exaggerated pressure response (i.e., SBP > 200 mmHg) during exercise testing. In hypertensive subjects, an exceeding upward pressure in response to physical activity can predict an increase in cardiovascular mortality and morbidity, regardless of resting BP values[63]. Kasiakogias et al[64] found a higher frequency of exaggerated BP response during exercise testing in subjects with OSA and systemic hypertension, compared to hypertensive patients without respiratory sleep disorders. In our study group, no cases of exaggerated responses were found and no differences in peak BP values were detected between t0 and t1. However, we have documented that baseline BP values are associated with exercise tolerance, as shown by the negative correlation between 24-hour mean SBP and Tlim. Nonetheless, we did not find correlations between CPET parameters and OSA severity indices[65,66]. This study has several limitations. Firstly, sample size is underpowered and there is an evident unbalanced females/males ratio, favoring the latter. Secondly, no control group was available to compare the effects of CPAP between patients with and without concurrent RH. Finally, measurement of BP during exercise testing was performed with manual non-invasive methods, with the risk of low accuracy in registering BP values.

Conclusions

Our data demonstrate that six-month long treatment with CPAP reduces significantly clinic BP and 24-hour mean SBP and DBP values among patients with OSA-related RH. CPAP therapy improves endothelial dysfunction and early markers of atherosclerosis, as shown by the significant improvement in IMT and RRI. CPET is a simple procedure that has great potential for prognostic evaluation among hypertensive patients. We are the first to show that CPAP therapy increases exercise tolerance in terms of endurance time among patients with OSA and RH. Furthermore, in our study group, we found that the lower the control of BP values, the lower the exercise tolerance in patients naive from CPAP. Further studies are needed in this population to evaluate the effects of longer intervals of ventilation therapy. Particularly interesting would be to assess the benefits from CPAP in a specific group of patients, newly diagnosed with RH before the onset of irreversible cardiovascular damage.

Conflict of Interests

On behalf of all authors, the corresponding author states that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper. The manuscript has been seen and approved by all the authors. This study was not funded. The manuscript is not under consideration for publication elsewhere. The results presented in this paper have not been published previously in whole or part, except in abstract format. The authors declare that they have no conflict of interest.

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