

Long-term gender-specific evolution of blood pressure under CPAP therapy in hypertensive patients with obstructive sleep apnea syndrome

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Abstract

Introduction: Reduction of blood pressure (BP) under CPAP treatment in patients with obstructive sleep apnea syndrome (OSAS) associating hypertension (HT) is controversial and short-term evolution is often measured using the sphygmomanometer.

Purpose: To study the variation in BP (sphygmomanometer and Holter) after 3 and 6 months of CPAP in OSAS patients associating hypertension.

Methods: We applied the exclusion criteria (hypoventilation, respiratory diseases, secondary hypertension, antihypertensive treatment modification during study, non-compliance) on 96 consecutive patients (SPSS 17.0: Chi test, T-test).

Results: 15 hypertensive patients (8.53 years from diagnosis) with OSAS succeeded six months of following: 3 women (20%), 12 men (80%) were comparable as age, body mass index and Epworth score; women had more severe OSAS. Sphygmomanometer measuring in men showed a decrease in systolic BP (SBP) (142 ± 8.9 to 128.7 ± 11.7 mmHg, $p=0.005$) and diastolic BP (DBP) (82 ± 11.9 to 69.1 ± 6.6 mmHg, $p=0.040$) at three months of treatment. Women had no changes at 3 and 6 months of assessment using the sphygmomanometer. BP Holter showed no significant changes in men; women exhibit a significant increase in maximum DBP/24 hours (104 ± 13.4 to 169.5 ± 27.5 mmHg, $p=0.034$) and mean daytime DBP/24 hours (100 ± 14.1 to 166 ± 32.5 mmHg, $p=0.046$) from 3 to 6 months. No group presents dipper status change to 3 or 6 months.

Conclusions: The trend in both groups of increase in BP for 3 to 6 months is explained by the natural evolution of an old HT history. Long time monitoring using Holter device is more accurate in assessing cardiovascular risk.

Keywords: obstructive sleep apnea syndrome, arterial hypertension, CPAP treatment

Rezumat

Evoluția specifică pe termen lung a valorilor tensionale sub tratament CPAP în funcție de gen la pacienții hipertensivi cu sindrom de apnee în somn

Introducere: Reducerea tensiunii arteriale (TA) sub tratamentul CPAP la pacienții cu sindrom de apnee în somn obstructiv (SASO) ce asociază hipertensiune arterială (HTA) este controversată și evoluția pe termen scurt este adesea urmărită utilizând sfingomanometrul.

Scop: Studiarea variației TA după 3 și 6 luni de CPAP (sfingomanometru și Holter), la pacienții cu SASO asociind HTA.

Metodă: Am aplicat criteriile de excludere (hipoventilație, patologii respiratorii, HTA secundară, modificarea tratamentului antihipertensiv pe perioada studiului, non-compliance) unui număr de 96 de pacienți consecutivi (SPSS 17.0: Chi test, T-test).

Rezultate: 15 pacienți cu SASO hipertensivi de 8,53 ani au încheiat controlul de 6 luni: 3 femei (20%), 12 bărbați (80%), fiind comparabili ca vârstă, indice de masă corporală și scor Epworth; femeile au SASO mai sever. TA măsurată cu sfingomanometrul la bărbați arată scăderea TA sistolice (TAs) ($142 \pm 8,9$ la $128,7 \pm 11,7$ mmHg, $p=0,005$) și diastolice (TAd) ($82 \pm 11,9$ la $69,1 \pm 6,6$ mmHg, $p=0,040$) doar la 3 luni de tratament. Femeile nu au avut modificări la 3 și 6 luni la evaluarea cu sfingomanometrul. TA măsurată Holter a arătat la bărbați absența modificărilor semnificative; femeile prezintă o creștere semnificativă de la 3 la 6 luni a valorii maxime TAd/24h ($104 \pm 13,4$ la $169,5 \pm 27,5$ mmHg, $p=0,034$) și a TAd diurne medii/24h, ($100 \pm 14,1$ la $166 \pm 32,5$ mmHg, $p=0,046$). Nici un grup nu prezintă modificarea statusului dipper la 3 sau 6 luni.

Concluzii: Tendința în ambele grupuri de creștere a valorilor TA de la 3 la 6 luni este explicată prin evoluția naturală a unei HTA vechi. Urmărirea îndelungată cu ajutorul Holterului este mai precisă în evaluarea riscului cardiovascular.

Cuvinte-cheie: sindrom de apnee în somn obstructiv, hipertensiune arterială, tratament CPAP

Introduction

Obstructive sleep apnea syndrome (OSAS) is defined by the presence of more than five respiratory events (apnea or hypopnea) per hour of sleep, lasting more than 10 seconds. Apnea is a total cessation of airflow and hypopnea represents a more than 50% reduction in airflow from the initial amplitude¹.

OSAS is highly prevalent among the general population, occurring in 2-4% of adults with excessive daytime sleepiness², but having a much higher prevalence in adults without excessive daytime sleepiness, namely in 9% of women and 24% of men³. Depending on the surveyed population, this prevalence can soar to 50% in women and 80% in men diagnosed with morbid obesity⁴.

Hypertension (HT) is defined by values > 140 mmHg of systolic blood pressure (SBP) and/or > 90 mmHg of diastolic blood pressure (DBP)⁵.

OSAS associating HT is common, as the two diseases share the same risk factors (such as smoking, obesity). OSAS is responsible for nighttime HT and for the absence of a 10-15% decrease in blood pressure (BP) at night compared to daytime values, a model known as a non-dipper pattern⁵ in the specialized literature. Today, OSAS is recognized as one of the main causes for secondary HT⁶ and an independent risk factor in the occurrence of cardiovascular events^{7,8}. A series of studies have demonstrated that OSAS is an independent risk factor in the occurrence of HT^{9,10}.

CPAP (continuous positive airway pressure) is the treatment of choice for obstructive sleep apnea patients, improving nighttime respiratory events. Given the physiopathology mechanisms whereby OSAS may lead to an increase in blood pressure (sympathetic activity increase, activation of the renin-angiotensin-aldosterone system, higher oxidative burden as a result of repeated hypoxxygenation-reoxygenation cycles), treating OSAS would allegedly have a positive impact on BP values. However, the CPAP effect on lowering BP is controversial^{11,12}, with sometimes contradictory outcomes. Most surveys have shown minor decreases in BP values, with both BP measuring method and patient follow-up period playing an important role¹³. Nevertheless, when it comes to patients with multiple cardiovascular risk factors, a relatively limited decline in BP values can be perceived as clinically significant (for instance, a 5 mmHg drop in DBP lowers the stroke risk by 34% and the ischemic heart disease risk by 21%¹⁴). The heterogeneity of studies in the literature has prevented a consensus regarding the drug therapy and the use of CPAP in patients with OSAS associating HT.

In the existing literature, we found no studies that assess gender influence on BP variations in patients with OSAS and HT. This study is intended to identify gender-related differences in the evolution of OSAS and HT patients in terms of BP decrease under long-term (6 months) CPAP therapy, measuring BP values both by sphygmomanometer and by Holter monitoring over a 24-hour period.

MATERIAL AND METHOD:

General population surveyed

Between January 2011 and March 2012, we observed 96 consecutive patients who came to ward III of the "Marius Nasta" Pneumology Institute and were diagnosed with HT and suspected of OSAS. Only 19 of these 96 patients met the inclusion-exclusion criteria and agreed to sign the informed consent form, then were included in the study. Patients were monitored over a six-month period. The inclusion criteria were the presence of OSAS (diagnosed after manual validation of polygraphies and polysomnographies), HT (diagnosed prior to inclusion in the study), stable antihypertension treatment, unchanged for at least one month prior to registration in the study, manually validated CPAP

titration, acceptance and use of CPAP for an optimum duration (minimum four hours per night). The exclusion criteria included: secondary HT (causes other than OSAS), mild OSAS (that didn't require CPAP therapy), overlap syndrome, obesity-hypoventilation syndrome, other sleep disorders (narcolepsy, cataplexy, insomnia etc.), change in the hypertensive medication during the study, refusal or discontinuation of the CPAP therapy, CPAP therapy failure, stroke or acute myocardial infarction in the three months prior to the inclusion in the study, any kind of cancer at any time during the screening or follow-up, absence or withdrawal of the informed consent. The study was approved by the Institute's ethics commission. Out of the 19 patients, one was excluded for changing the antihypertensive medication during the study, another one for poor compliance; there was one patient who withdrew his consent and another one was excluded after being diagnosed of lung cancer during the study.

Blood pressure

The hypertension diagnosis was made either before they came to the Pneumology Institute (the patients were already undergoing treatment at the first clinical assessment) or when they arrived at our department, based on the ESH/ESC criteria. The appropriate therapy was thus established and newly diagnosed patients were re-evaluated one month after starting the treatment and included in the study.

BP values were office measured by sphygmomanometer during the initial exam, prior to the positive diagnosis of sleep apnea syndrome. The sphygmomanometer measurements were done in accordance with the guidelines⁶, using a proper cuff for obese patients.

Outpatient BP monitoring over 24 hours (Holter) was done only for patients subsequently diagnosed with moderate to severe OSAS (AHI $> 15/h$). Blood pressure was measured every 15 minutes during the day and every 30 minutes during the night. Once the initial evaluation (T0) was complete, the patients were put on both CPAP and drug therapy (unchanged antihypertensive treatment) and were assessed after 3 and 6 months of treatment (T3, T6).

Sleep study

A Viasys polygraph and an Alice 5 polysomnograph were used to diagnose OSAS and the records were made between 10 pm and 6 am. These two types of investigation shared the following channels: nose piece for the airflow, a microphone to record snoring, thoraco-abdominal belts, position sensor, pulse oximeter to register oxygen saturation and heart rate. Furthermore, the polysomnograph provided electroencephalogram, electrooculogram and electromyogram and was used in cases when the polygraph diagnosis was inconsistent with the clinical suspicion or when other associated sleep disorders were suspected.

Study protocol

The hypertensive patients were asked about their medical history, answered specific questionnaires, were subject to a clinical exam and were initially evaluated through BP measurements by sphygmomanometer, a

chest X-ray, an electrocardiogram (ECG), a spirometry and an ENT exam. The OSAS diagnosis was made on the first night spent in the sleep laboratory, in the presence of more than five respiratory events such as apnea or hypopnea, per hour of sleep, both respiratory events being accompanied by desaturation (more than 3-4% decrease of oxygen saturation from baseline). The apnea-hypopnea index (AHI) sums up all breathing disruptions per hour of sleep; an AHI =15-30/h describes a moderate OSAS and an AHI > 30/h describes a severe OSAS. After the first night of diagnosis, the patient were subject to CPAP titration in the sleep laboratory (GoodKnight 420G and REMstar Plus were used), making sure that each titration was optimum¹⁵. Manual titration was intended to improve the respiratory events (post-titration residual AHI ≤ 10/h), with patients tolerating CPAP pressure very well.

The patients were assessed at one, three and six months into the treatment (T1, T3, T6) based on OSAS symptoms, excessive daytime sleepiness (Epworth score), body mass index (BMI), blood pressure measured by sphygmomanometer and CPAP compliance, then at three and six months of treatment (T3, T6) based on OSAS symptoms, excessive daytime sleepiness (Epworth score), body mass index (BMI), blood pressure measured by sphygmomanometer and Holter and CPAP compliance.

Statistical analysis

The statistical analysis was done in the SPSS program, release 17.0. The qualitative variables were expressed in percentages, while the continuous variables were expressed as mean and standard deviation (SD). T and Chi tests were applied to assess the data, comparing baseline values with values at one, three and six months of CPAP treatment.

Results

Fifteen patients with OSAS associating HT completed the study and were evaluated at six months. Upon inclusion in the study, the following were assessed: anthropometric indexes (including BMI), HT history, daytime sleepiness (as OSAS symptom and independent cardiovascular risk factor, measured by the Epworth score; the Epworth score measures the risk of falling asleep in given situations; patients scoring below 10 had no daytime sleepiness, while those with a score ≥10 were considered to have severe daytime sleepiness), office blood pressure measured by sphygmomanometer and 24 hours measuring by Holter device, AHI measured by sleep study. The characteristics of the group are presented in Table 1.

Table 2 shows the differences between the two surveyed groups (women versus men in terms of certain anthropometric data, sleepiness, OSAS severity and BP values at the moment of inclusion in the study, with BP values assessed both by office and Holter measuring).

The statistical analysis of men/women differences revealed only one statistical difference which was detected in the initial AHI, as women had a significantly

Table 1

Main characteristics of the surveyed group at T0

Parameter	Value
Mean age (years)	60.40 ± 12.17
Percentage of men (%)	80%
BMI (kg/m ²)	34.41 ± 6.27
Mean Epworth score	10.2 ± 4.56
Mean AHI (events/hour of sleep)	53.82 ± 24.40
Mean AHI, post-titration (events/h)	7.52 ± 3.20
Mean CPAP (cmH ₂ O)	9.90 ± 1.51
Percentage of stage III HT, ESH/ESC	86%
Time since declared HT diagnosis (years)	8.53 ± 7.14
Mean SBP (mmHg)*	143 ± 11.30
Mean DBP (mmHg)*	82.33 ± 10.83
Mean SBP (mmHg)**	148.60 ± 19.30
Mean DBP (mmHg)**	82.60 ± 11.58
Dipper status (%)	40%

* measured by sphygmomanometer; ** measured by Holter 24h.

BMI=body mass index, AHI=apnea-hypopnea index, CPAP=continuous positive airway pressure, HT=hypertension, SBP=systolic blood pressure, DBP=diastolic blood pressure

higher AHI (79/h versus 48/h, $p=0.032$), but there were no differences in the two surveyed groups after the CPAP titration (Table 2). As for the BP values, there were no statistically significant differences with regard to measurements done in the office (by sphygmomanometer) and by Holter device (Table 2).

There were no significant BP changes in either group at one month (T1) (Figures 1, 2a, 2b). Also, the compliance was similar between the groups (6.24 ± 0.97 h/day in women, 6.23 ± 1.22 h/day in men, $p=NS$) and residual AHI was also similar (2.90 ± 1.68 /h for women, 4.77 ± 2.94 /h for men, $p=NS$).

After three months of treatment, there were no differences in terms of CPAP compliance, which was 6.23 ± 1.05 h/day in women, 6.20 ± 1.02 h/day in men, $p=NS$ and residual AHI after three months was similar (2.60 ± 0.98 /h for women, 3.92 ± 2.56 /h for men, $p=NS$). CPAP therapy compliance after six months of treatment indicated a mean CPAP use time of 5.89 ± 0.87 h/day in women, 6.14 ± 0.97 h/day in men ($p=NS$), with a residual AHI of 2.70 ± 0.98 /h for women and 4.16 ± 2.37 /h ($p=NS$). Neither compliance, nor residual AHI varied significantly from baseline ($p=NS$).

Table 2 Men/women differences at T0

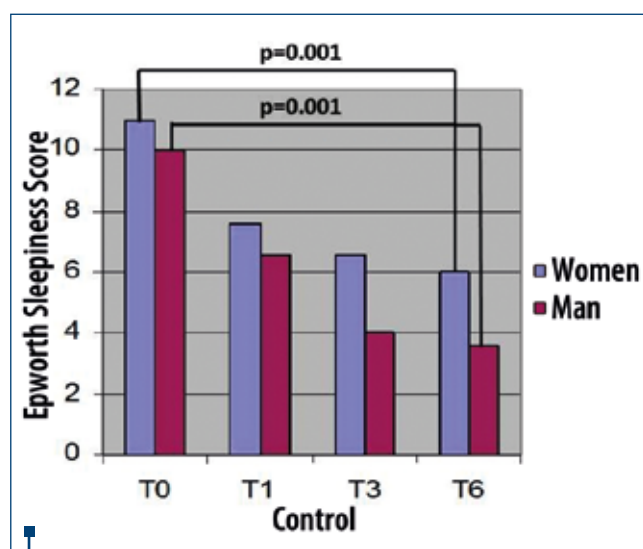
Parameter	Value in women	Value in men	P
Age (years)	59.02 ± 10.74	61.57 ± 12.61	NS
BMI (kg/m ²)	36.03 ± 5.74	35.09 ± 6.56	NS
Mean Epworth score	11 ± 4.58	10.00 ± 4.93	NS
Mean AHI (events/h)	79.73 ± 24.72	48.11 ± 19.54	0,032
Mean AHI, post-titration (events/h)	5.23 ± 2.58	9.05 ± 4.27	NS
Mean CPAP (cmH ₂ O)	10.66 ± 1.52	9.62 ± 1.50	NS
Mean SBP (mmHg)*	143.67 ± 10.81	142.08 ± 8.90	NS
Mean DBP (mmHg)*	83.33 ± 5.77	82.08 ± 11.95	NS
Mean SBP (mmHg)**	147.33 ± 31.72	148.91 ± 17.05	NS
Mean DBP (mmHg)**	82.33 ± 16.04	82.66 ± 11.13	NS
Dipper status (%)	41.66%	33.33%	NS

(*measured by sphygmomanometer; ** measured by Holter 24h.

BMI=body mass index, AHI=apnea-hypopnea index, CPAP=continuous positive airway pressure, SBP=systolic blood pressure, DBP=diastolic blood pressure)

Table 3 Changes in the dipper pattern under CPAP therapy

Sex	Dippers T0	Dippers T3	P (T3-T0)	Dippers T6	P (T6-T3)	P (T6-T0)
Men	33.3%	46.6%	NS	20%	NS	NS
Women	41.6%	20%	NS	10%	NS	NS


Figure 1. Trend of Epworth score under CPAP therapy

Neither women, nor men gained any weight after one month, according to the BMI ($35.76 \pm 5.41 \text{ kg/m}^2$ versus $33.49 \pm 6.17 \text{ kg/m}^2$, $p=\text{NS}$). The body mass index didn't change at subsequent exams either, with values of $35 \pm 5.35 \text{ kg/m}^2$ in women versus $33.28 \pm 6.00 \text{ kg/m}^2$ in men, $p=\text{NS}$ after three months and $33.35 \pm 7.28 \text{ kg/m}^2$ versus $32.63 \pm 7.04 \text{ kg/m}^2$, $p=\text{NS}$ after six months; the BMI values had no statistically significant variations from baseline.

At the three-month assessment (T3), we detected a statistically significant drop of both SBP and DBP in men, sphygmomanometer measurements, from 142 ± 8.9 to $128.7 \pm 11.7 \text{ mmHg}$, $p=0.005$ and from 82 ± 11.9 to $69.1 \pm 6.6 \text{ mmHg}$, $p=0.040$, respectively; there were no statistically significant differences in sphygmomanometer measurements after six months of CPAP treatment (T6), but we detected a statistically insignificant increase of the values (Figures 2a, 2b). The women group

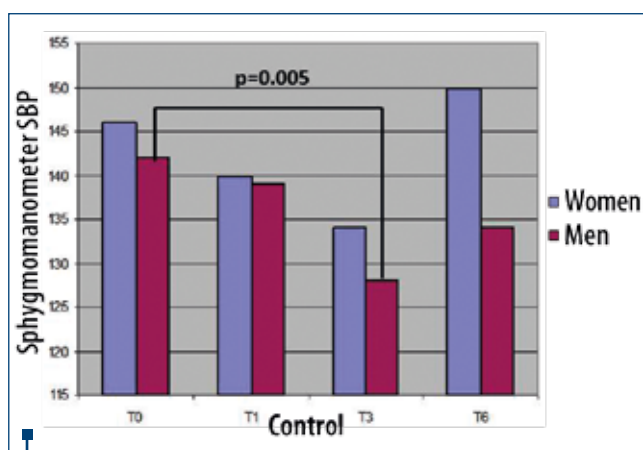


Figure 2a. Trend of SBP measured by sphygmomanometer

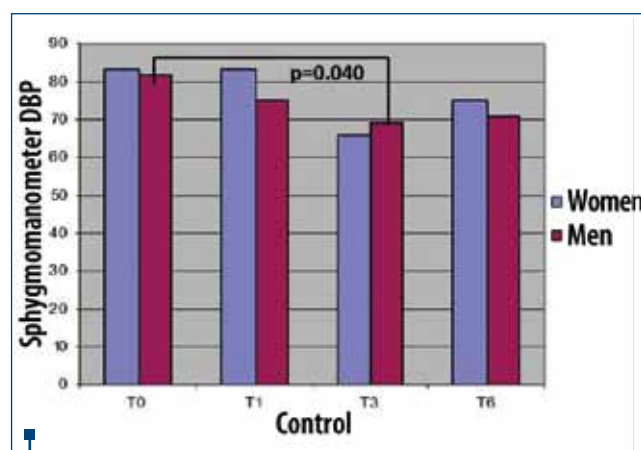


Figure 2b. Trend of DBP measured by sphygmomanometer

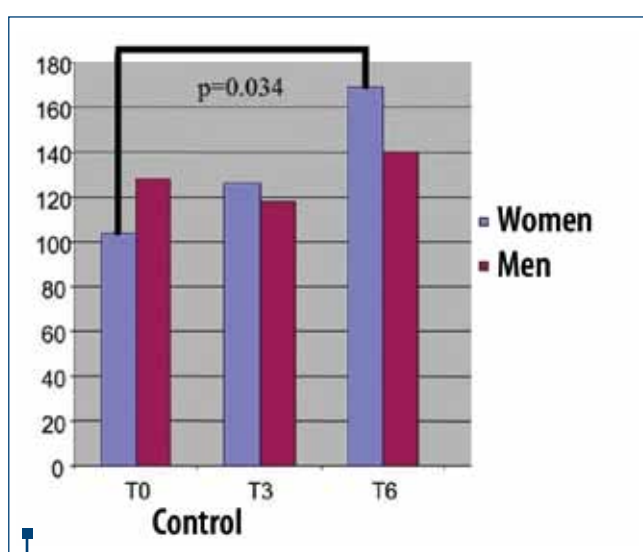


Figure 3. Trend of maximum DBP values/24h

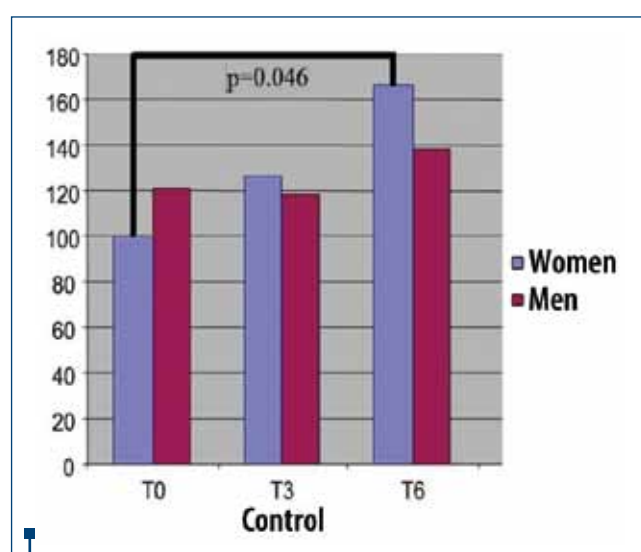


Figure 4. Trend of mean daytime DBP values

presented no significant changes at three months (T3) or at six months (T6) in terms of sphygmomanometer measurements, but the same statistically irrelevant downward trend with subsequent increase (Figures 2a, 2b) was detected.

No statistically significant changes in BP values measured with Holter 24h were identified in the men's group (Figures 3, 4). A statistically significant increase of the maximum DBP is seen in women, from an initial 104 ± 13.4 to 169.5 ± 27.5 mmHg after six months of CPAP treatment, $p=0.034$ (Figure 3). The group of women also reported a statistically relevant increase, namely the mean value of daytime DBP for 24 hours, from 100 ± 14.1 initially to 166.0 ± 32.5 mmHg after six months of CPAP, $p=0.046$ (Figure 4). As for the values that experienced statistically significant changes in the group of women, with a progressive upward trend from baseline at three and six months, the analysis of the group of men revealed the same statistically not significant trend of initial decrease at three months, then increase at six months to values higher than baseline (similar to values measured by sphygmomanometer).

The dipper pattern of Holter values showed no statistically significant changes from baseline neither at three, nor at six months of CPAP therapy, with a statistically irrelevant upward trend of the dipper percentage of men at three months and a downward trend in women, followed by a slight decrease in both groups, but without returning to the initial values (Table 3).

The decline of the Epworth score was constant and statistically relevant, starting from the initial exam until the 6-month assessment, from 10 ± 4.93 to 3.63 ± 1.40 , $p<0.001$ (Figure 1).

Discussions

We conducted a prospective study on a group of patients with OSAS associating HT, over a 6-month period from starting the CPAP therapy. The number of patients who met the inclusion and exclusion criteria and took the treatment for six months was 15. The men/women ratio (2.33:1) was similar to the descriptions in the literature, with OSAS more prevalent in men.

The blood pressure decrease was present only in sphygmomanometer measurements (systolic and dias-

tolic) at three months (statistically relevant for men only), then values tended to increase despite the favorable evolution of OSAS, according to the clinical exam and residual AHI (although no gain of weight or lowering in compliance were noted). Holter 24h values indicated an increase from baseline at three and then at six months in the female population (regarding certain parameters, even with statistical significance) and a downward trend in the male population at three months, followed at six months by an increase to values higher than baseline.

The percentage of dippers showed no favorable evolution either, being lower than baseline at six months, although men presented a statistically insignificant decrease at three months.

The lower percentage of women with dipper status at three and six months of CPAP therapy indicates a higher cardiovascular risk associated with the non-dipper status in their case. The fact that women blood pressure didn't decrease under CPAP therapy, considering the non-dipper status as well, could be due to a number of co-morbidities.

The small size of the group (only 15 patients) and the prevalence of men in the surveyed group may influence the outcome, but a subsequent study conducted by the

same group of authors on a similar population of only hypertensive patients who took no anti-hypertension medication indicated the same BP increase at six months and a trend of lower blood pressure values at 12 months¹⁶. This phenomenon can be explained by the stress of adjusting to the CPAP device and by the natural evolution of an existing HT.

Conclusions

Women, in particular, demonstrated an increase in DBP and in the non-dipper pattern from three to six months, attributable to the stress of adjusting to the CPAP device, to perhaps more co-morbidities and the natural progress of a long-term diagnosed HT. Considering the hormonal differentiation between men and women, the differences can be real and should be confirmed by subsequent studies that cover a wider group of women.

Given that Holter BP measurements are undoubtedly much more accurate in defining the cardiovascular risk associated with OSAS and eliminate a series of confusing factors (for instance, white-coat hypertension), we conclude that long-term Holter monitoring is essential to identifying the effect of CPAP on HT. ■

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