Positive pressure therapy in patients with cardiac arrhythmias and obstructive sleep apnea

Giorgiana Nicoleta Dediu[1,2], Ștefan Dumitrache-Rujinski[1,3], Răzvan Lungu[2], Sabina Frunză[2], Camelia Diaconu[1,2], Daniela Bartoș[1,2], Miron Alexandru Bogdan[1,3]

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest

2. Department of Internal Medicine, Emergency Hospital, Bucharest

3. "Marius Nasta" Pneumology Institute of Bucharest

Correspondence:
Dr. Giorgiana Dediu,
Department of Internal Medicine, Emergency Hospital,
Floreasca street, No. 8, 6th floor, Bucharest.
e-mail: drgiorgiana.dediu@gmail.com

Abstract

Background. *Positive pressure therapy (CPAP) in patients with cardiac arrhythmias and obstructive sleep apnea (OSAS) may have favorable effects by correcting intermittent hypoxemia and sympathetic activation.*
Objective. *To assess the effect of CPAP added to pharmacological treatment in the rate control and prevention of arrhythmias recurrence in patients with OSA.*
Materials and methods. *Prospective, interventional study study which included patients diagnosed with OSAS (cardiorespiratory polygraphy, AHI>5/hour), and arrhythmias (ECG, Holter ECG), divided in two groups: group A (pharmacological therapy only) and group B (pharmacological therapy and CPAP). The patients were evaluated at enrollment (T_0), at 3 and 6 months (T_3 and T_6) regarding the type, severity and recurrence of cardiac arrhythmias.*
Results. *36 patients (31 men), mean age: 63.2 ± 12 years were enroled. In group A: 7 patients with ventricular extrasystoles, 8 with permanent atrial fibrillation, 1 patient with atrial flutter and 2 patients with paroxystic supraventricular tachycardia. In group B: 8 patients with ventricular extrasystoles, 5 with permanent atrial fibrillation, 2 patients with recurrent episodes of atrial fibrillation and 3 with paroxystic supraventricular tachycardia. A positive correlation (r: 0.74, p <0.001) between Oxygen Desaturation Index and AHI was found. At T6, 12 patients from group B, and 18 from group A were evaluated. In group B, the mean heart rate in patients with atrial fibrillation was 69/min., lower than in group A (82/min.), no cases with recurrent atrial fibrillation were found, and more patients with class II Lown ventricular extrasystoles passed in class I Lown, compared to group A. In group B, heart rate statistically correlated with AHI (r: 0.53, p <0.005).*
Conclusion. *In patients with OSAS, adding CPAP to pharmacological therapy has favorable effects on preventing recurrences, heart rate control in patients with atrial fibrillation and in reducing frequency and/or severity of ventricular extrasystoles.*
Keywords: *cardiac arrhythmias, obstructive sleep apnea, CPAP therapy*

Rezumat

Terapia cu presiune pozitivă la pacienții cu aritmii cardiace și Sindrom de Apnee în Somn de tip Obstructiv
Introducere. *Terapia cu CPAP la pacienții cu aritmii cardiace și Sindrom de Apnee în Somn de tip obstructiv (SASO) poate avea efecte favorabile prin corectarea hipoxemiei intermitente și activării simpatice.*
Obiectivul lucrării. *Evaluarea efectului terapiei cu presiune pozitivă (CPAP) asociată terapiei farmacologice în controlul frecvenței și prevenția recurenței aritmiilor la pacienții cu SASO.*
Material și metodă. *Studiu prospectiv, interventional, în care au fost incluși pacienți diagnosticați cu SASO (poligrafie cardio-respiratorie, IAH>5/ora) și aritmii (EKG repaus, Holter EKG) structurați în două grupuri: grupul A (terapie farmacologică) și grupul B (terapie farmacologică asociată CPAP). Pacienții din cele două grupuri au fost evaluați la includerea în studiu (T_0), la 3 și 6 luni (T_3 și T_6) privitor la tipul, severitatea si recurența tulburărilor de ritm cardiac.*
Rezultate. *Au fost studiați 36 pacienți (31 bărbați), vârsta medie 63,2±12 ani. În grupul A: 7 pacienți cu extrasistolie ventriculară (EV), 8 cu fibrilație atrială permanentă (FiA), unul cu flutter atrial, doi cu tahicardie paroxistică supraventriculară (TPSV). In grupul B: 8 cu EV, 5 cu FiA, 2 cu istoric de fibrilație atrială recurentă, 3 cu TPSV. Indexul de Desaturare s-a corelat pozitiv cu Indexul de Apnei Hipopnei (r: 0.74, p <0.001). La T6 au fost evaluați 12 pacienți din grupul B și 18 din grupul A. În grupul B, frecvența cardiacă medie la pacienții cu FiA a fost de 69 /min., mai mică decât în grupul A (82/min.), nu s-a constatat recurența FiA și semnificativ mai multi pacienți cu EV au trecut din clasa II în clasa I Lown comparativ cu grupul A. În grupul B, frecvența cardiacă s-a corelat semnificativ statistic cu IAH (r: 0.53, p <0.005).*
Concluzii. *La pacienții cu SASO, terapia cu CPAP asociată terapiei farmacologice are efecte favorabile asupra prevenirii recurențelor, controlului frecvenței cardiace la pacienții cu FiA și scăderea severității extrasistoliei ventriculare.*
Cuvinte-cheie: *aritmii cardiace, sindrom de apnee în somn de tip obstructiv, CPAP*

Introduction

Obstructive sleep apnea syndrome (OSAS), an increasingly diagnosed condition, is accompanied by multiple cardiovascular consequences, one of them being cardiac arrhythmias (especially nocturnal).

OSAS is defined by recurrent episodes of decrease / absence of oro-nasal airflow, in the presence of thoraco-abdominal movements and snoring during sleep.

Older studies showed a prevalence of OSAS in active adult population (30-60 years) of 4% in men and 2% in women, if an Apnea Hypopnea Index (AHI: number of apnea and hypopnea per hour of sleep) greater than 10 per hour and daytime sleepiness is used to define the presence of the OSAS. Currently, symptomatic OSAS prevalence is estimated at 3-7% in men and 2-5% in women[1], varying by race and ethnicity, being higher in African Americans younger than 35 years compared to Caucasians of the same age[2,3].

Obesity is the main risk factor in OSAS; in patients with morbid obesity (BMI>40 kg/m^2) OSAS prevalence exceeds 90%.

The recurrence of apneas and hypopneas lead to intermittent hypoxemia and increased sympathetic activity.

Intermittent hypoxemia, the response to hypoxic stimulus and the increased level of catecholamines are etiopathogenic factors for cardiovascular disease. Repetitive oxidative stress is responsible for systemic inflammation and for cardiac remodeling, which is one of the causes of atrial fibrillation in this population[4]. Severe hypoxemia is an etiologic factor for ventricular arrhythmias and sudden death.

The most common arrhythmias in patients with OSAS are bradycardia and asystole during sleep (lasting less than 10 seconds)[5] and were found in 18% of patients with severe OSAS[6]. The first association between OSAS and atrial fibrillation was made in 1983 in an observational study including 400 patients with moderate / severe OSAS that were monitored by ECG[7]. It was observed that 3% of patients developed paroxysmal nocturnal arrhythmias. The prevalence of OSAS in patients with atrial fibrillation is around 30-80%[8,9]. The literature showed that OSAS is a risk factor for recurrent atrial fibrillation after ablation or cardioversion. In a meta-analysis that included six observational studies, the diagnosis of OSAS increased the risk of recurrent atrial fibrillation after ablation by 25%[10]. Another observational study that included 130 patients with atrial fibrillation and electric conversion showed that the rate of recurrence of atrial fibrillation in patients with untreated OSAS was 82%, in patients with treated OSAS was 42% and 53% in those without OSAS [11]. Also, OSAS is more common in patients with atrial fibrillation than in those who associate other cardiovascular conditions[12].

Continuous Positive Air Pressure (CPAP) represents the golden standard therapy for patients with severe / moderate OSAS and its role is to maintain the upper airway open during inspiration, acting basically as a pneumatic splint[13]. Stopping the pathophysiological chain induced by the succession of apneas and hypopneas makes the addition of CPAP to the pharmacological therapy in patients with OSAS and cardiac arrhythmias logical.

Study objective

The objective of the study was to assess the effect of CPAP added to pharmacological treatment on the rate control and prevention of arrhythmias recurrence in patients with OSA.

Materials and methods

Prospective, interventional, in-progress study started in June 2013, which included 36 patients, with a mean age of 63.2 ± 12 years, diagnosed with **OSAS** by 6 channels cardiorespiratory polygraphy (Stardust II Philips-Respironics®): nasal air flow (pressure cannula), thoraco-abdominal movements, continuous pulse oximetry, body position, snoring, and **cardiac arrhythmias** evidenced by ECG and Holter ECG (CardioSpy EC-2H®). Patients were included into two groups: 18 patients in group A, which received antiarrhythmic drug therapy and 18 patients in group B, with pharmacological therapy associated to CPAP (CPAP use at least 5 hours per night).

The inclusion criteria in the study were:

- high pre-test suspicion of OSAS (apneas reported by entourage, snoring, daytime sleepiness, obesity)
- cardiac arrhythmias: permanent atrial fibrillation, documented history of paroxysmal atrial fibrillation, ventricular extrasystoles (VES), other arrhythmias: paroxysmal supraventricular tachycardia (PSVT), atrial flutter.

The exclusion criteria: patients who did not sign the informed consent, patients with craniofacial malformations, patients with neuropsychiatric or thyroid disorders, hemodynamically unstable patients, alcoholics and drug users.

The study design included three visits:

1. $\mathbf{T_0}$, inclusion of patients in the study. During the visit were peformed: anamnesis (including history of smoking), clinical examination (anthropometric indices: height, weight, **Body Mass Index (BMI)**, neck circumference, waist to hip ratio), cardiorespiratory polygraphy, ECG, Holter ECG, oxyhaemoglobin saturation (SaO_2), arterial blood gases (ambient air, at rest), serum lipid profile.

2. $\mathbf{T_3}$, 3 months after inclusion in the study, when we downloaded CPAP device memory card (average residual AHI, effective mean pressure, number of hours of use, non-intentional air leaks). Holter ECG was also performed.

3. $\mathbf{T_6}$, 6 months from the start. The protocol from T_0 was reapplied and CPAP efficacy assessed.

Definitions

AHI: number of apneas and hypopneas per hour of recording.

Hypopnea was scored as follows: oxyhemoglobin diminution in air flow amplitude by 50% and 3% desaturation. Apnea (total absence of airflow) and hypopnea last for at least 10 seconds.

Oxygen Desaturation Index (ODI): number of significant oxyhemoglobin desaturations (from baseline), per hour of recording. The cut-off for significant desaturation was set at 3%.

OSAS severity (AHI)

- Mild OSAS: 5-15 /hour
- Moderate OSAS: 15-30 /hour
- Severe OSAS: >30 /hour

Permanent atrial fibrillation (AF) is an atrial fibrillation lasting a year or more.

Paroxysmal supraventricular tachycardia (PSVT) includes any tachyarrhythmia that requires the atrium and/or the atrioventricular node for initiating and maintaining it.

Lown classification for ventricular extrasystoles. (Table 1).

Statistical analysis

Data processing was done using Microsoft Excel 2010 and the Statistical Analysis System (SAS) 9.1. The results were expressed as mean ± standard deviation or as an absolute number (percentage). Variables were normally distributed, using Pearson correlation index.

T-test was used to analyse the parameters resulting from the estimation of the linear regression model; the statistical model was validated using the coefficient of determination (R square).

Table 1 Lown classification for ventricular extrasystoles (VES)

Lown classification	Arrhythmia
Grade 0	No ventricular extrasystoles
Grade I	Unifocal and infrequent VES; <30 VES per hour
Grade II	Unifocal and frequent VES, ≥30 VES per hour
Grade III	Multifocal VES
Grade IVA	2 consecutive beats (couplets)
Grade IVB	≥3 consecutive beats (salvos)
Grade V	"R on T" phenomenon

Table 2 Patients characteristics at T0

GROUP	A	B
Age (years)	62 ± 13.74	63.28 ± 10.64
Men / Women (n)	15/3	16/2
Smokers (n)	14	8
BMI (kg/m²)	36.87 ± 5.8	30.52 ± 3.1
Diabetes (n)	2	7
Epworth (x/24)	10.6 ± 4.37	9.4 ± 4.16
ODI (x/hour)	36.1 ± 22.53	34.86 ± 15.56
AHI (x/hour)	39.83 ± 18.1	34.7 ± 17.3
Lowest SaO_2 (%)	83.25 ± 2.85	83.65 ± 5.06
Paroxysmal FA (n)	8	–
Recurrent FA (n)	–	2
Permanent FA (n)	–	5
PSVT (n)	2	3
Atrial flutter (n)	1	–
VES (n)	7	8

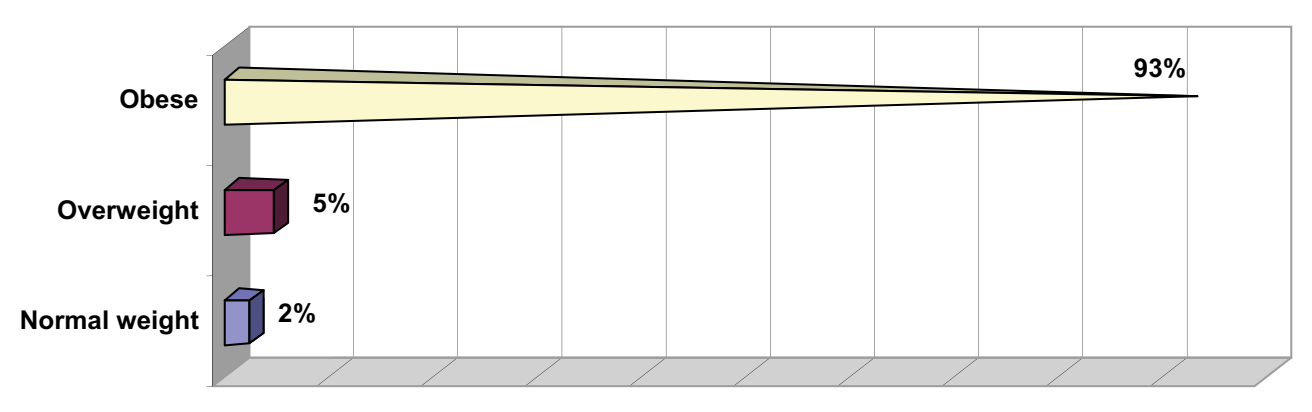

Figure 1. *Distribution of BMI in pacients included in the study*

Results and discussion

The characteristics of the 36 patients at enrollment regarding: age, gender, smoking history, Body Mass Index (BMI), AHI, oxygen desaturation index (ODI), lowest oxyhemoglobin saturation (SaO_2) and cardiac arrhythmias are presented in Table 2.

A predominance of males (86%) and obese patients (93%) (Figure 1) may be noted. This is similar to the data from the literature, obesity and male gender representing the main risk factors for OSAS[1]. Obesity represents also a major confounding factor in establishing OSAS independent role in cardiovascular pathology.

25% of the studied patients had diabetes, a condition frequently associated with obesity, but also with the metabolic syndrome induced by OSAS[14]. Most patients (61%) were smokers, a recognized risk factor for coronary heart disease, but also for sleep apnea[15,16].

At T_0, the patients had daytime sleepiness, due to sleep fragmentation induced by repeated episodes of apneas and hypopneas, with arousals and consecutive sympathetic activation, which play a pathogenic role in the development of nocturnal heart rhythm disorders.

The main cardiac arrhythmia diagnosed at T_0 in our patients was represented by VES: 15 patients (41%), followed by paroxysmal AF: 8 patients (22%) and PSVT: 5 patients (13%). 7 patients (19%) had permanent AF or a history of documented AF recurrence (Figure 2).

The prevalence of cardiac arrhythmias was reported to increase with the severity of OSAS[17,18]. In our study, about 60% of patients with severe OSAS had cardiac arrhythmias (Figure 3).

The prevalence of OSAS in our patients increases with age, a finding also reported by other epidemiological studies[19] (Figure 4).

In group B, at T_0, a statistically significant positive correlation (r:0.74, p<0.001) between the Oxygen Desaturation Index: **ODI** (a marker of intermittent hypoxemia, which is recognized to play a pathogenic role in the development of cardiovascular and metabolic complications)[20] and **AHI** was found. Both are a consequence

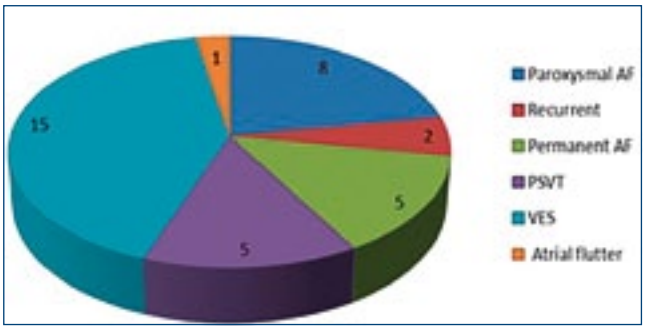

Figure 2. *Type of cardiac arrhythmias in patients included in the study (T0)*

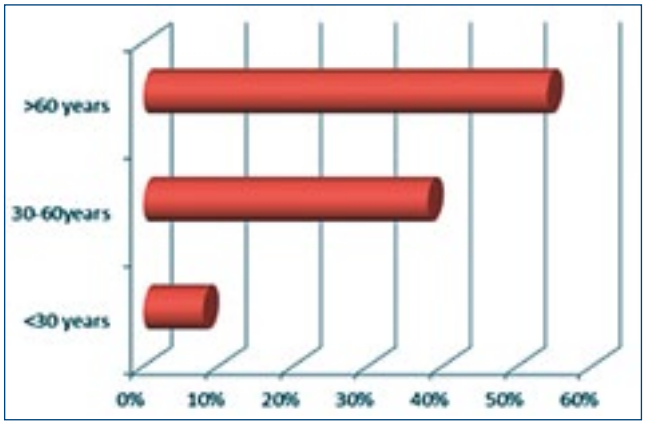

Figure 4. *OSAS severity by age categories*

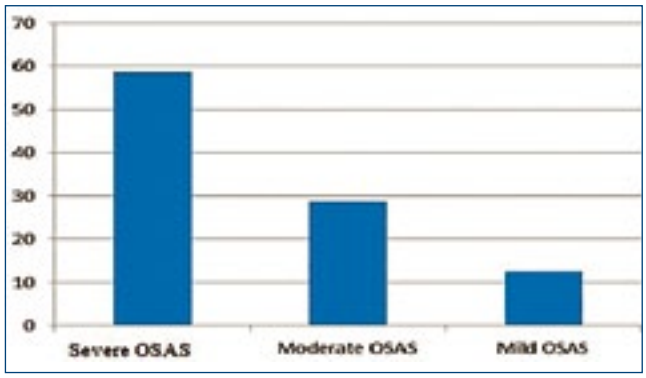

Figure 3. *Prevalence of cardiac arrhythmias increase with the severity of OSAS*

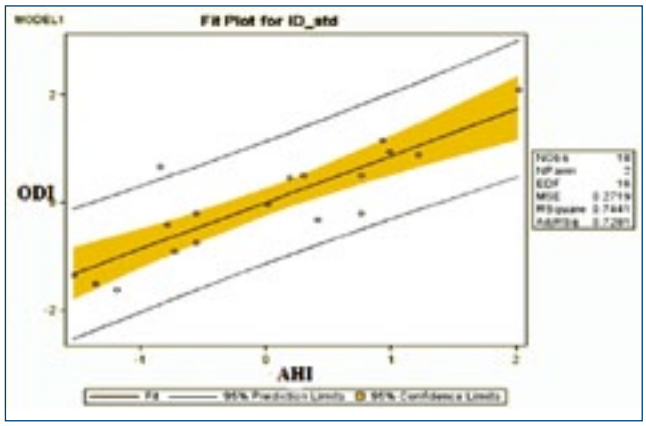

Figure 5. *Correlation between Oxygen Desaturation Index (ODI) and AHI at T0 in group B (r: 0.74; p<0.001)*

of repeated episodes of nocturnal respiratory events (Figure 5). At the end of the study, 12 patients in group B and 18 in group A were evaluated.

The Epworth Sleepiness Questionnaire is used to evaluate daytime sleepiness in different situations, with a score varying between 0 (total absence of sleepiness) and 24 (falling asleep)[21]. At T_0, the patients in group B had an average Epworth score of 9.4 ± 4.16; after 6 months of CPAP therapy, the average Epworth score was 7.42 ± 2.14, a lower value, but not reaching the statistical significance (small number of patients). This may be explained by the diminution of episodes of nocturnal respiratory events (apneas and hypopneas) and lack of sleep fragmentation with CPAP therapy.

In group B, 12 patients (67%) continued to use CPAP correctly (at least 4 hours per night in more than 70% of nights). Patients who used CPAP did not have recurrent AF, experienced a decrease in the number and severity of VES (passed from class II to class I according to Lown classification) and a lowering of mean heart rate in those with permanent AF.

At T_6, in patients with AF, the mean heart rate was 82/min. in group A, and 69/min. in group B, a lower value, but not reaching the statistical significance (Table 3). Also, it was noticed that at T_6, the mean heart rate was considerably lower than at T_0 only in group B (Table 3).

In group B, a statistically significant positive correlation (r:0.53, p<0.005) between heart rate and AHI at T_6 was found (Figure 7).

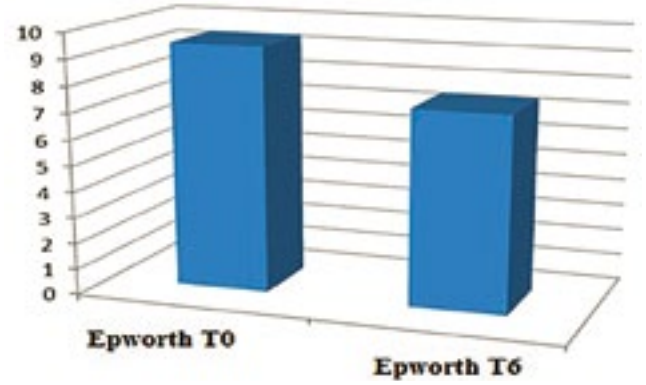

Figure 6. *Average value of Epworth questionnaire at T_0 and T_6 in group B*

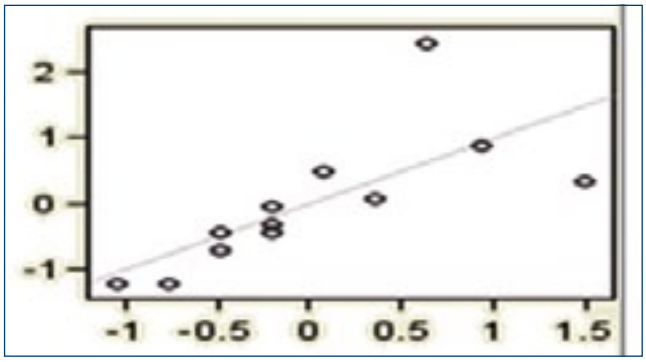

Figure 7. *Correlation between heart rate and AHI at T_6 in group B (r: 0.53; p<0.005)*

Table 3 Cardiac frequency in patients with AF at T_0, T_3, T_6 in groups A and B.

	Group A		Group B	
	mean	standard deviation	mean	standard deviation
Heart rate T_0	84	19	95	20
Heart rate T_3	81	18	77	14
Heart rate T_6	82	19	69	8

Conclusions

Our study found a correlation between oxygen desaturation index, apnea hypopnea index and the presence of heart rhythm disorders, supporting the involvement of intermittent hypoxemia and sleep fragmentation / sympathetic activation in etiopathogenesis of cardiovascular complications in OSAS.

The majority of patients with heart rhythm disorders had moderate or severe OSAS. We found that the greater the value of AHI, the higher was the mean heart rate in patients with atrial fibrillation.

In patients with OSAS, adding CPAP to the pharmacological therapy has favorable effects on preventing recurrences, heart rate control in patients with atrial fibrillation and decrease in frequency and/or severity of ventricular extrasystoles.

Evaluating the presence of OSAS in patients with clinical suspicion (obesity, daytime sleepiness, apneas reported by entourage) and associated cardiac rhythm disturbances is important, since there is an increasing body of evidence that proper use of CPAP therapy offers additional benefits to pharmacological therapy.

Study limits

There was a small number of patients that completed the evaluation (study still in progress, preliminary results).

The diagnosis of OSAS was performed by six channels cardiorespiratory polygraphy and not by polysomnography (golden standard). However, the patients included in the study had high pretest probability for OSAS, in which case the diagnostic with cardiorespiratory poligraphy is accepted.

AutoCPAP technology was used to establish the appropriate effective pressure, and autoCPAP devices were employed for further therapy of OSAS. There are data that report that effective pressure variation during the night would induce secondary subcortical arousals with residual diurnal sleepiness and sympathetic stimulation. ■

References

1. E Lindberg. Epidemiology of OSA. In McNicholas W, Bonsignore M. European Respiratory Society Monograph 2010; 50 (Sleep Apnoea): 51-68.
2. Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. *Am J Respir Crit Care Med.* 1997 Jan;155(1):186-92.
3. Ancoli-Israel S, Klauber MR, Stepnowsky C, Estline E, Chinn A, Fell R. Sleep-disordered breathing in African-American elderly. *Am J Respir Crit Care Med*. 1995 Dec;152(6 Pt 1):1946-9
4. Jennum P, Riha RL .Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. *Eur Respir J.* 2009;33(4):90
5. Simantirakis EN, Schiza SI, Marketou ME, Chrysostomakis SI, Chlouverakis GI, Klapsinos NC, Siafakas NS, Vardas PE. Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder. *Eur Heart J.* 2004;25(12):1070
6. Rossi VA, Stradling JR, Kohler M. Effects of obstructive sleep apnoea on heart rhythm. *Eur Respir J.* 2013 Jun;41(6):1439-51.
7. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA.* 2004; 291(16):2013.
8. Gami AS, Friedman PA, Chung MK, Caples SM, Somers VK. Therapy Insight: interactions between atrial fibrillation and obstructive sleep apnea. *Nat Clin Pract Cardiovasc Med.* 2005;2(3):145
9. Porthan KM, Melin JH, Kupila JT, Venho KK, Partinen MM. Prevalence of sleep apnea syndrome in lone atrial fibrillation: a case-control study. *Chest*. 2004;125 (3):879.
10. Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. *Am J Cardiol.* 2011 Jul;108(1):47-51.
11. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, Shamsuzzaman AS, Somers VK. Obstructive sleep apnea and the recurrence of atrial fibrillation.*Circulation*. 2003;107(20):2589.
12. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of Atrial Fibrillation and Obstructive Sleep Apnea. *Circulation.* 2004; 110(4): 364-7.
13. Montserrat J.M, Navajas D, Parra O, Farré R. Continuous positive airway pressure treatment in patients with OSA. *Eur Respir Mon* 2010;50:250-273
14. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2009;32 :S62-S67.
15. Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. *Thorax* 1991; 46: 85-90.
16. Wetter DW, TB Y, Bidwell TR, et all. Smoking as a risk factor for sleep -disordered breathing. *Arch Intern Med* 1994; 154 ; 2219-2224.
17. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM Sleep-disordered breathing and mortality: a prospective cohort study. *SOPLoS Med.* 2009;6(8):e1000132
18. Martínez-García MA, Campos-Rodríguez F, Catalán-Serra P, Soler-Cataluña JJ, Almeida-Gonzalez C, De la Cruz Morón I, Durán-Cantolla J, Montserrat JM. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study. *Am J Respir Crit Care Med.* 2012 Nov 1;186(9):909-16.
19. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age of sleep apnea in men: I.Prevalence and severity. *Am J Respir Crit Care* 1998; 157:144-148
20. Remmers JE, DeGroot WJ, Sauerland EK, et all. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol.*1978; 44; 931-938.
21. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540