Rhinology, 46, 144-150, 2008

Short-term CPAP treatment induces a mild increase in inflammatory cells in patients with sleep apnoea syndrome*

Szymon Skoczyński, Mariola Ograbek-Król, Maciej Tażbirek, Aleksandra Semik-Orzech, Władysław Pierzchała

Department of Pulmonology, Medical University of Silesia, Katowice, Poland

SUMMARY

Background: *Nasal CPAP has been proven to be an efficient method of treating SAS patients without facial dysmorphism. However, it still remains a matter of debate why it is not universally well tolerated.*

The ***aim of the study*** *was to evaluate the influence of initial CPAP treatment on nasal function in SAS patients.*

Patients and methods: *Forty-two patients were consecutively included in a prospective clinical study and divided into the three following groups:*

1) *SAS subjects (26 patients qualifying for CPAP treatment),*
2) *First control group (C1) (9 patients with mild or moderate SAS, not willing to be treated with CPAP, AHI >5 [n/h]),*
3) *Second control group (C2) (7 healthy subjects, AHI ≤ 5).*

Nasal patency was measured by active anterior rhinomanometry (AAR) at recruitment and after a three-day CPAP treatment. After each AAR nasal lavage was obtained from both nostrils. Total inflammatory cell count (TCC) in each nasal lavage was then calculated in a Neubauer's chamber.

Results: *Initial CPAP treatment caused a statistically significant rise of TCC in nasal lavage of SAS patients, when compared with initial values [n*10^5*/ml] (pre: 1,30, post: 1,92, p = 0,009). No significant differences (p > 0,05) were found both in initial TCC and nasal patency values among the three studied groups.*

Conclusions: *SAS subjects present an unchanged nasal patency when compared to control subjects. Initial CPAP therapy might be responsible for evoking local nasal inflammation.*

Key words: SAS, CPAP, rhinomanometry, nasal lavage

INTRODUCTION

Sleep apnoea syndrome (SAS) is a growing problem in most well-developed countries. In a middle age population SAS is defined as five or more episodes of apnoea or hypopnoea per hour of sleep [(1)]. To fulfil the internationally accepted criteria, each apnoea or hypopnoea incident must be at least ten seconds long. According to the most often cited study, SAS is present in 4% of male and 2% of the female population [(2)].

Clinically, SAS is characterized by recurring apnoeas and hypopnoeas during sleep, leading to blood desaturation, sleep fragmentation and many cardio-vascular complications [(2)]. Nose obstruction, caused by local nasal inflammation has generally been accepted as one of SAS initializing factors [(3)]. Up till now, CPAP treatment has been considered as the gold standard in SAS treatment in patients who do not complain of nasal obstruction and do not have evidence of anatomical upper airway obstruction. Clinical data show, that CPAP treatment is not well tolerated by all patients and it is difficult to predict which patients will not accept this kind of treatment.

Although some studies tried to evaluate the impact of decreased nasal patency on SAS incidence, as well as on the effectiveness of CPAP treatment, the exact pathophysiological mechanism in patients without nasal symptoms has not been

Footnote: Abbreviations: AHI - apnoea hypopnoea index (number of apnoeas and hypopnoeas during one hour of sleep), BMI - body mass index, CPAP - continuous positive airway pressure, RNT Bex - nasal expiratory resistance in both nostrils modo Broms, RNT Bin - nasal inspiratory resistance in both nostrils modo Broms, RNT Sex - standard nasal expiratory resistance in both nostrils, RNT Sin - standard nasal inspiratory resistance in both nostrils, SAS - sleep apnoea syndrome, TCC - total cell count (in 1 ml of nasal lavage).

*Received for publication: October 28, 2008; accepted: February 7, 2008

established yet [4]. It is probably caused by the fact, that both, in SAS and nose function diagnosis, different measuring tools are used, some of which are still not well-standardized: anterior, posterior or acoustic nasal rhinomanometry, rhinoscopy or cephalometric measurements. On the other hand, some other methods useful in the diagnosis of these disorders, like computed tomography, are expensive and include radiation exposure. Nasal patency, its disturbances and main mechanisms of impairment are important in predicting patient's future compliance with CPAP therapy. There is evidence of local inflammation existence in nares of SAS patients [5]. The authors showed that the above-mentioned patients have increased local neuthrophilia, as well as elevated markers of systemic inflammation (increased plasma levels of CRP, IL-6, and IL-18 [6]). On the other hand, there is also evidence that a 4-week intranasal fluticason therapy significantly lowers AHI in some patients with rhinitis and SAS [7]. This could be evidence, that inhibition of local inflammation in those patients might improve the parameters of nose function. Some epidemiological studies show a correlation between the degree of nasal patency and nostril swelling caused by snoring [8] or the degree of nasal patency and snoring index in patient's medical history [9]. Attempts to correlate the degree of nasal obstruction and sleep disordered breathing were less successful [8,9]. In most cited articles nasal patency was measured in a sitting position [9], while there is strong evidence that the supine position predisposes to its obstruction, by lowering nasal volume [10]. That is the reason why we decided to use rhinomanometry in the supine position. There is evidence of elevated nasal resistance in SAS patients, although the direct pathomechanism of this phenomenon has not been established yet [5,11]. It has been proven that, treating nasal obstruction might reduce obstructive sleep apnoea severity by decreasing mouth breathing during sleep [12]. It has also been proven that nasal resistance rises in subjects being exposed to dry cold air, or other irritating factors. In recent publications evidence that CPAP without humidifier does not impair cilary function and mucosal epithelium transport has been shown, however, the small number of patients enrolled (n=8) makes this result questionable [13]. Published articles tend to indicate different mechanisms of nasal obstruction in SAS patients like: local inflammation or swelling, caused by accelerated nasal blood flux [14]. Divergent data have also been published about the dominant inflammation type identified on nasal examination [15,16]. There is also some evidence that nasal mucosa inflammatory changes occur with advancing age, leading to worsening of SAS symptoms and difficulty tolerating CPAP, when used without humidification [17,18]. On the basis of these data it is difficult to analyze the precise mechanisms of increased nasal resistance in SAS patients. It is hard to decide whether SAS is evoked by elevated nasal resistance or also by nasal obstruction, as other SAS symptoms influence each other causing symptom worsening.

The aim of our study was to asses the impact of a few-day CPAP therapy on nasal patency and the number of inflammatory cells in nasal lavage of SAS patients. We compared the SAS group treated with CPAP to healthy subjects and to patients with mild SAS who did not accept to be treated by CPAP. The question was if there were any differences between SAS patients treated with CPAP and the two control groups, as far as nose function parameters and nasal cellularity were concerned. We hypothesized, that initial CPAP therapy in some of the patients might induce local nasal inflammation, explaining subsequent lack of compliance.

MATERIAL AND METHODS

Study population

A total of 59 patients from the Pulmonary Department of the Medical University of Silesia, were prescreened for the study. Of these, 42 patients (age between 18 and 65) fulfilled all entry criteria and were eligible for randomization into one of the three following groups:

1. Group of 26 SAS subjects (8% female, 92% male, aged 27 to 55 years, mean age 50,2); in which SAS was diagnosed on the basis of AHI value of $>$ 5 [n/h] (mean AHI: 35,8 $\pm$ 18,4) and the concurrent clinical symptoms of SAS such as: excessive day time sleepiness, disrupted sleep, night choking, apnoeas during sleep witnessed by bed partner.
2. Control group I (56% female, 44% male, aged 38 to 65 years, mean age 52,0) – including 9 subjects diagnosed with SAS (AHI value of $>$ 5 [n/h]); (mean AHI: 12,0 (6,0 - 22,2) who refused CPAP treatment. All nine subjects gave no consent for CPAP treatment, either because of relatively little intensity of clinical symptoms of SAS, or aversion to constant CPAP usage. All of them were thoroughly informed about the possible consequences of refusing such treatment; the importance of body mass reduction was highlighted and/or laryngological examination in order to consider the usefulness of potential surgical treatment. To all nine subjects it was also suggested to repeat polisomnography after 6-12 months.
3. Control group II (29% female, 71% male, aged 26 to 54 years, mean age 50,0) – including 7 healthy controls, in which SAS occurrence has been excluded (AHI value of $\leq$ 5 [n/h] (mean AHI: 3,0 (0,0 - 5,0); no clinical symptoms of SAS).

The exclusion criteria were as follows: 1) age below 18 and over 65, 2) smoking history during 6 months before entering the study, 3) history of upper airway infection for 4 weeks prior to the preliminary visit and in course of the study, 4) anatomical anomalies (such as deviated nasal septum) or previous nasal or sinus surgery, that made it impossible to carry out AAR, 5) receiving any topical and systemic medication that might affect nasal patency or local nasal mucosa inflammation (systemic or topical glucocorticosteroids, histamine-receptor antagonists, cromoglycate, ketotifen, mast cell stabilizing drugs and topical decongestants) for 4 weeks prior to the preliminary visit and in course of the study.

Study design

The study complied with the principles of the Declaration of Helsinki and its protocol was approved by the Bioethical Committee of the Silesian Medical University. All patients gave their written informed consent for the investigation.

During the preliminary visit, complete medical history was taken and a clinical examination was performed. All subjects were also asked to complete both the questionnaire for evaluating the probability of SAS occurrence and the Epworth scale. All subjects were prescreened with a polysomnographic screening device (STARDUST - Respironiks), performed according to the standard protocol [19]. To avoid the introduction of bias, patients with AHI $<$ 5 were asked to undergo full night polysomnography. All subjects checked thus again had, as previously, AHI $<$ 5.

On the basis of their history, clinical examination and the results of multi channel sleep screening device all subjects were further randomized into one of the three studied groups.

The following diagnostic procedures were then performed:

In the group of SAS subjects – active anterior rhinomanometry and nasal lavage were performed twice: at baseline and after a three-day CPAP treatment. In both control groups, active anterior rhinomanometry and nasal lavage were performed only during the preliminary visit.

Rhinomanometry

Before starting the procedure, subjects were acclimatized and kept lying flat on their backs for 15 min. AAR was performed, according to the recommendations of Committee Report on Standardization of Rhinomanometry [20] in a lying position. An active anterior rhinomanometer (Rhinotest MP 500, EVG Electronic-Vertriebs-GmbH, Germany) with foam rubber nose adapters and a transparent anaesthetic rubber mask was used. The flow-pressure curves were plotted on-line on the screen and the measurement was repeated until a stable curve was obtained during quiet breathing with the mouth closed. For each nostril, a rhinomanogram was recorded which related inspiratory and expiratory nasal airflow to transnasal pressure. The resistances of the left and right cavity separately were calculated from the flow in the fixed gradient pressure of 75 Pa as the average of 6 consecutive breaths.

Nasal lavage

Nasal lavage was performed by the „nasal pool" technique as described by Greiff and coworkers [21]. Six ml of warm, sterile saline were instilled into the left and right nasal cavity for 5 min. and then, by decompression, recovered into the plastic syringe. The mean proportion of lavage fluid recovered was 67,0% ± 3,2%. Nasal lavage fluid was processed immediately after being recovered. Lavage sample was shaken vigorously to break up clumps of mucus and 0,1ml of 0,1% dithiothreitol (Gibco BRL, Warsaw, Poland) was added. Centrifugation (5 min. at 500g) of saline washings separated cell pellet and supernatant. The supernatant was discarded and the obtained sediment was suspended in 1 ml of sterile phosphate buffered saline (PBS, Sigma). After staining the cells with the Kimura method, the total number of non-squamous cells was counted with the use of a Neubauer hemocytometer, allowing determination of the number of cells in 1 ml of recovered fluid.

Statistics

The statistical evaluation was performed with a statistical software package (Statistica 6.0). Results are expressed as mean values ± SD or medians and ranges (maximal and minimal values are in brackets). The Kolmogorov-Smirnov test was used to test variables for normal distribution. Depending on the distribution, Student *t* test, Wilcoxon signed-rank test or Kruskal-Wallis test were used for inter-group comparisons. Pre-post

Table 1. General characteristics of study subjects.

	Subjects with SAS n=26	**Control group I n=9**	**Control group II n=7**	**p***
Age [years]	50,2 (27,0-55,0)	52,0 (38,0-65,0)	50,0 (26,0-54,0)	NS
Sex F [%]	92	44	71	-
BMI	31,4 (21,3-50,0)	29,3 (23,6-38,1)	28,3 (25,3-36,0)	NS
WHR	1,0 (0,9-1,1)	0,9 (0,8-1,1)	1,0 (1,0-1,1)	NS
AHI	36,3 (11,0-71,0)	12,0 (6,0-22,2)	3,0 (0,0-5,0)	$<$ 0,001
O_2 sat [%]	80,0 (50,0-91,0)	87,0 (71,0-90,0)	84,0 (77,0-89,0)	0,026
CPAP [mbar]	9,0 (4,0-12,0)	ND	ND	-

Data are expressed as medians and ranges (maximal and minimal values are in brackets).

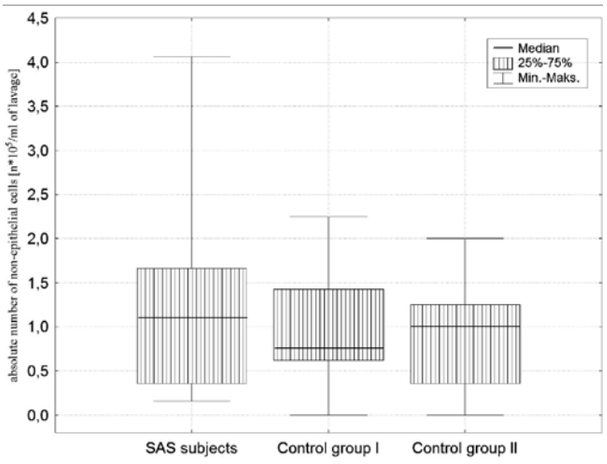
*p value for inter-group comparisons (Kruskal-Wallis test)

F – females, BMI – body mass index, WHR – waste to hip ratio, AHI –apnoea and hypopnoea index, O_2 sat- average minimal saturation achieved during screening polysomnography, CPAP –continuous positive airway pressure, ND – Not Done, NS – Non significant.

Table 2. Comparison of initial values of rhinomanometric parameters between studied groups.

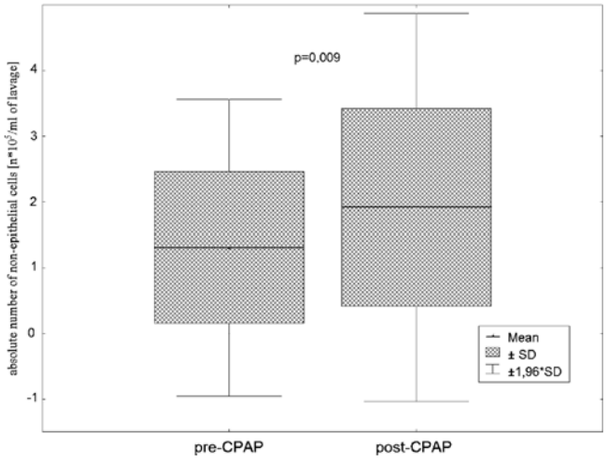
Rhinomanometric parameter [Pa]	Subjects with SAS	Control group I	Control group II	p*
RNT Sex	0,29 (0,09-0,78)	0,31 (0,26-0,52)	0,22 (0,12-1,03)	NS
RNT Sin	0,28 (0,02-3,33)	0,33 (0,31-0,68)	0,24 (0,17-1,40)	NS
RNT Bex	0,15 (0,02-3,02)	0,27 (0,01-0,95)	0,14 (0,01-1,60)	NS
RNT Bin	0,18 (0,01-3,77)	0,33 (0,01-0,76)	0,15 (0,03-2,81)	NS

Data are expressed as medians and ranges (maximal and minimal values are in brackets).
*p value for inter-group comparisons (Kruskal-Wallis test), RNT Sex - standard nasal expiratory resistance in both nostrils, RNT Sin - standard nasal inspiratory resistance in both nostrils RNT Bex - nasal expiratory resistance in both nostrils modo Broms, RNT Bin - nasal inspiratory resistance in both nostrils modo Broms, NS – Non significant.



The inter-group comparison of baseline lavage total cell count revealed no significant differences between the three studied groups ($p > 0,05$, Kruskal-Wallis test).

Figure 1. Comparison of initial nasal lavage cellularity in studied groups.



Short-term CPAP treatment significantly increased nasal lavage cellularity of SAS subjects when compared to baseline values (pre-post comparison, Student t test).

Figure 2. Evolution of total non-epithelial cell count in nasal lavage of SAS subjects after initial CPAP treatment.

treatment differences were evaluated, depending on the distribution, using Student *t* test or Wilcoxon test. P values of $< 0,05$ were accepted as statistically significant.

RESULTS

Main baseline characteristics of the included patients are summarized in Table 1. Twenty-six subjects with SAS that underwent CPAP treatment, 9 SAS subjects that refused CPAP treatment and 7 healthy controls were enrolled in the study. All studied groups were comparable in respect to age, BMI and WHI values. When compared to control groups, at entry, subjects with SAS exhibited significantly higher AHI ($p < 0,001$; Kruskal-Wallis test), and average minimal blood saturation values during night screening ($p = 0,026$; Kruskal-Wallis test).
On average, effective CPAP pressure values of 9,0 (4,0 - 12,0) [mbar] were applied in the first group of SAS subjects. The mean value of AHI achieved after initial CPAP treatment was within physiological range, averaging 4,83 ± 3,38. This proves that the applied treatment was highly effective.

No statistically significant differences were found between rhinomanometric parameters at baseline between all groups (Table 2). In the group of SAS subjects, CPAP treatment did not induce any significant changes in any of the rhinomanometric parameters (Table 3).

No statistically significant differences were found in the total non-epithelial cell count in nasal lavage between the studied groups at baseline ($p = 0,907$; Kruskal-Wallis test) (Figure 1). In the group of SAS subjects CPAP treatment induced a statistically significant increase of 47% in the number of non-epithelial cells in the nasal lavage, as compared to baseline [$n*10^5$/ml

Table 3. Evolution of rhinomanometric parameters induced by initial CPAP treatment in group of SAS subjects.

Rhinomanometric parameter [Pa]	Pre-CPAP	Post-CPAP	p*
RNT Sex	0,29 (0,09-0,78)	0,29 (0,09-0,88)	NS
RNT Sin	0,28 (0,02-3,33)	0,28 (0,02-2,16)	NS
RNT Bex	0,15 (0,02-3,02)	0,15 (0,01-1,13)	NS
RNT Bin	0,18 (0,01-3,77)	0,16 (0,02-2,08)	NS

Data are expressed as medians and ranges (maximal and minimal values are in brackets).

*P value for pre-post comparisons (Student t test), CPAP - continuous positive airway pressure, RNT Sex - standard nasal expiratory resistance in both nostrils, RNT Sin - standard nasal inspiratory resistance in both nostrils RNT Bex - nasal expiratory resistance in both nostrils modo Broms, RNT Bin - nasal inspiratory resistance in both nostrils modo Broms, NS – Non significant.

of lavage]: (pre-treatment values: 1,30 ± 1,15; post-treatment values: 1,92 ± 1,51; p = 0,009; Student t test) (Figure 2).

DISCUSSION

To start our discussion it is necessary to explain the cut-off point (AHI value of ≤ 5 [n/h] accepted by our team for sleep apnoea. As mentioned before, we have accepted the diagnostic criteria by the American Academy of Sleep Medicine Task Force [1]. However, it should be stressed, that there are also other criteria based on different AHI cut-off points (5, 10, 15) used by different authors to diagnose SAS. The reason for such discrepancies is the variability in scoring hypopnoea, which also complicates between-study comparisons. In most cases SAS is effectively treated with nasal CPAP. CPAP is considered as a well-accepted method of treatment in SAS patients without nose obstruction [22]. Patients with nasal obstruction or anatomical abnormalities of the facial skeleton should undergo surgical treatment. SAS patients often complain of nasal symptoms before and during CPAP. This might be the result of increased nasal resistance, which predisposes to upper airway obstruction and consequently to snoring [23]. There is also evidence that CPAP treatment might be responsible for symptoms such as running nose and sneezing [24]. Our findings are partly consistent with the above. However, as nasal patency of SAS subjects did not change during our study, the increased cell count after CPAP treatment could have been an effect of pre-existing disease. To minimize this possibility we excluded subjects with history of rhinorhea or nasal obstruction. We have also excluded patients treated with systemic and/or local drugs, which might potentially interfere with nasal function and influence CPAP usage compliance, such as systemic or topical glucocorticosteroids, histamine-receptor antagonists, cromoglycate, ketotifen, mast cell stabilizing drugs and topical decongestants. Some authors [24] compared different nasal function parameters after 6 months of CPAP usage. In our research we decided to assess the nasal function after three days of CPAP therapy. We were fully aware that this relatively short observation time might be considered as one of the study limitations. However, we wanted to avoid possible influence of seasonal factors (e.g. pollens, upper respiratory tract infections) on nasal patency and potential local inflammation. However, this relatively short observation period of three days has not been completely free from other interfering factors, such as an increased risk of upper airway nosocomial infection. In contrast to some other published studies [25] in which the authors used mainly paranasal X-ray, CT and anterior rhinoscopy, our study aimed to assess nasal function using AAR. CPAP with humidifiers were not used in our study, as it has been proven that humidifiers significantly reduce upper airway side effects and lead to better CPAP compliance [18]. Instead of completing full night polysomnography - the golden standard in SAS diagnosis - in our study we have used multi channel sleep studying devices, as it has been proven that they can accurately make a diagnosis of SAS when daytime symptoms coexist [19]. To minimize this as a potential source of methodological bias, we have asked patients without SAS (AHI ≤ 5 [n/h]) - as confirmed by multi channel screening device (STARDUST-by Respironics) - to additionally undergo a whole night polysomnography test (Alice 4, Respironics). In all of those cases (50% of subjects enrolled to control group 2) the diagnosis did not change. Increased nasal patency is not the only factor, which influences acceptance of CPAP therapy [26]. Other factors affecting CPAP compliance are: discomfort caused by the face mask, limitation in movements during sleep, claustrophobia, eye irritation by air leakage, allergy to the mask, effect on bed partners, relatively mild day time symptoms and many others that were not analyzed in the present study.

According to previous studies low AHI values may predict with high accuracy that CPAP will not be tolerated. We assume that this was a reason why some of the patients with mild to moderate SAS did not want to use CPAP. Patients enrolled in this group were discharged from the Pulmonary Department with the recommendation for laryngological treatment and active weight reduction. They were also requested to undergo follow up polysomnography after 6 to 12 months. In contrast to Sugiara et al. [26] acceptance of CPAP therapy in our patients correlated positively with AHI but not with nasal patency. In our study nasal patency and cell markers of nose inflammation were evaluated simultaneously. That is why our study, as a multi factor nasal control research, provides wider view on the analyzed problem than most of the studies previously published.

The presence of a systemic inflammatory state in SAS patients is well proven [27]. Scientists and clinicians agree that recurrent oxidative stress accelerates systemic inflammation in this pop-

ulation and leads to a metabolic syndrome characterized by atherosclerosis and shorter life expectancy. Cardio-vascular complications are one of the most frequent causes of death in this population [2].

A systemic inflammatory state is not the only manifestation of inflammation in the SAS population. Several authors seem to propose different mechanisms of cell and cytokine infiltration of the upper airways. The influence of an increased oxidative airway stress has been proven by increased levels of IL-6 and 8-Isoprostane in exhaled breath condensate in SAS subjects [28]. SAS children have a higher neutrophil concentration [29] as well as other inflammatory mediators such as leukotrienes and prostaglandins [30] collected from the upper airways. In contrast to systemic findings, the influence of CPAP treatment on local nasal inflammation has not been established yet. There is evidence that in some cases nasal CPAP may induce airway hyperresponsiveness [31]. There is also some data on local intranasal inflammation in SAS patients, which would explain the existence of upper airway obstruction in non-smoking SAS patients [4]. This is caused by an increased number of polymorphonuclear leukocytes and a high bradykinin concentration [4].

The significant changes found in lavage cellularity after initial CPAP treatment in SAS subjects open wider diagnostic and treatment possibilities in this disease. Further research including a longitudinal analysis of nasal lavage differential cell count and other inflammatory markers present in nasal secretions and blood, could help to elucidate the exact pathomechanisms responsible for poor CPAP compliance. Assessment of dominant inflammatory cell types in SAS patients would lead to diagnosing the exact pattern of inflammation and allow cause-specific treatment. Finally, some authors speculate that CPAP treatment reduces local and systemic inflammation [32]. This may suggest a role for a pharmacological method in SAS co-treatment. According to our findings, nasal CPAP treatment initially leads to local nasal inflammation. This fact requires further investigation and assessment during longer observation periods.

CONCLUSION

Initial CPAP treatment in SAS patients induces local inflammation documented by increased nasal lavage cellularity without concurrent nasal obstruction.

REFERENCES

1. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force Sleep 1999 1; 22: 667-689.
2. McNicholas WT, Bonsigore MR, Management Committee of EU COST ACTION B26. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 2007; 29: 156-178.
3. Kramer MF, de la Chaux R, Fintelmann R, Rasp G. NARES: a risk factor for obstructive sleep apnoea? Am J Otolaryngol 2004; 25: 173-177.
4. Rubinstein I. Nasal inflammation in patients with obstructive sleep apnoea. Laryngoscope 1995; 105: 175-177.
5. Staevska MT, Mandajieva MA, Dimitrov VD. Rhinitis and sleep apnoea. Curr Allergy Asthma Rep 2004; 4: 193-199.
6. Minoguchi K, Yokoe T, Tazaki T, et al. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnoea. Am J Respir Crit Care Med 2005 1; 172: 625-630.
7. Kiely JL, Nolan P, McNicholas WT. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. Thorax 2004; 59: 50-55.
8. Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. Thorax 1991; 46: 85-90.
9. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep-disordered breathing. The University of Wisconsin Sleep and Respiratory Research Group.
J Allergy Clin Immunol 1997; 99: 757-762.
10. Virkkula P, Maasilta P, Hytonen M, Salmi T, Malmberg H. Nasal obstruction and sleep-disordered breathing: the effect of supine body position on nasal measurements in snorers. Acta Otolaryngol 2003; 123: 648-654.
11. Li HY, Wang PC, Hsu CY, Cheng ML, Liou CC, Chen NH. Nasal resistance in patients with obstructive sleep apnoea. ORL J Otorhinolaryngol Relat Spec 2005; 67: 70-74.
12. McLean HA, Urton AM, Driver HS, et al. Effect of treating severe nasal obstruction on the severity of obstructive sleep apnoea. Eur Respir J 2005; 25: 521-527.
13. Bossi R, Piatti G, Roma E, Ambrosetti U. Effects of long-term nasal continuous positive airway pressure therapy on morphology, function, and mucociliary clearance of nasal epithelium in patients with obstructive sleep apnoea syndrome. Laryngoscope 2004; 114: 1431-1434.
14. Hayes MJ, McGregor FB, Roberts DN, Schroter RC, Pride NB. Continuous nasal positive airway pressure with a mouth leak: effect on nasal mucosal blood flux and nasal geometry. Thorax 1995; 50: 1179-1182.
15. Nandwani N, Caranza R, Hanning CD. Obstructive sleep apnoea and upper airway reactivity. J Sleep Res 1998; 7: 115-118.
16. Olopade CO, Christon JA, Zakkar M, et al. Exhaled pentane and nitric oxide levels in patients with obstructive sleep apnoea. Chest 1997; 111: 1500-1504.
17. Desfonds P, Planes C, Fuhrman C, Foucher A, Raffestin B. Nasal resistance in snorers with or without sleep apnoea: effect of posture and nasal ventilation with continuous positive airway pressure. Sleep 1998; 15: 625-632.
18. Massie CA, Hart RW, Peralez K, Richards GN. Effects of humidification on nasal symptoms and compliance in sleep apnoea patients using continuous positive airway pressure. Chest 1999; 116: 403-408.
19. Ballester E, Solans M, Vila X, et al. Evaluation of a portable respiratory recording device for detecting apnoeas and hypopnoeas in subjects from a general population. Eur Respir J 2000; 16: 123-127.
20. Clement PA, Gordts F; Standardisation Committee on Objective Assessment of the Nasal Airway, IRS, and ERS. Consensus report on acoustic rhinometry and rhinomanometry. Rhinology 2005; 43: 169-179.
21. Greiff, CEA 1990
22. Ballester E, Badia JR, Hernandez L, et al. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnoea/hypopnoea syndrome. Am J Respir Crit Care Med 1999; 159: 495-501.
23. Hudgel DW. The role of upper airway anatomy and physiology in obstructive sleep apnoea. Clin Chest Med 1992; 13: 383-398.
24. Brander PE, Soirinsuo M, Lohela P. Nasopharyngeal symptoms in patients with obstructive sleep apnoea syndrome. Effect of nasal CPAP treatment. Respiration 1999; 66: 128-135.
25. Lowe AA, Fleetham JA, Adachi S, Ryan CF. Cephalometric and computed tomographic predictors of obstructive sleep apnoea severity. Am J Orthod Dentofacial Orthop 1995; 107: 589-595.
26. Sugiura T, Noda A, Nakata S, et al. Influence of nasal resistance on initial acceptance of continuous positive airway pressure in treatment for obstructive sleep apnoea syndrome. Respiration 2007; 74: 56-60.

27. Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Tanaka A, Oda N, Okada S, Ohta S, Naito H, Adachi M. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnoea. Am J Respir Crit Care Med 2005; 172: 625-630.
28. Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ. 8-Isoprostane, a marker of oxidative stress, is increased in exhaled breath condensate of patients with obstructive sleep apnoea after night and is reduced by continuous positive airway pressure therapy. Chest 2003; 124: 1386-1392.
29. Li AM, Hung E, Tsang T, et al. Induced sputum inflammatory measures correlate with disease severity in children with obstructive sleep apnoea. Thorax 2007; 62: 75-79.
30. Goldbart AD, Krishna J, Li RC, Serpero LD, Gozal D. Inflammatory mediators in exhaled breath condensate of children with obstructive sleep apnoea syndrome. Chest 2006; 130: 143-148.
31. Devouassoux G, Levy P, Rossini E, et al. Sleep apnoea is associated with bronchial inflammation and continuous positive airway pressure-induced airway hyperresponsiveness. J Allergy Clin Immunol 2007; 119: 597-603.
32. Hatipoglu U, Rubinstein I. Inflammation and obstructive sleep apnoea syndrome pathogenesis: a working hypothesis. Respiration 2003; 70: 665-671.

Szymon Skoczyński MD
Department of Pulmonology
Medical University of Silesia
40-752 Katowice, ul. Medyków 14
Katowice
Poland

Tel: +48-50-251 9026
E-mail: simon.mds@poczta.fm