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ORIGINAL ARTICLE

C-reactive protein evolution in obstructive sleep apnoea patients under CPAP therapy

Sophia E. Schiza[*,1], Charalampos Mermigkis[†,1], Panagou Panagiotis[†], Izolde Bouloukaki[*], Eleftherios Kallergis[*], Nikolaos Tzanakis[*], Eleni Tzortzaki[*], Eleni Vlachaki[*] and Nikolaos M. Siafakas[*]

[*]Sleep Disorders Unit, Department of Thoracic Medicine, Medical School, University of Crete, Heraklion, Voutes, Greece, [†]Sleep Disorders Center, Pulmonary Department, 401 General Army Hospital, Athens, Greece

ABSTRACT

Background C-reactive protein (CRP) is recognized as a potential factor implicated in atherogenesis and associated cardiovascular morbidity. The aim of our study was to assess the CRP evolution during 1-year follow-up period in obstructive sleep apnoea (OSA) patients under CPAP treatment.

Methods Five hundred and twenty-eight patients with newly diagnosed moderate to severe OSA were included. CRP was assessed before CPAP initiation and at the 3rd, 6th and 12th month of the follow-up period. Patients were divided into good and poor CPAP compliance groups.

Results A significant reduction in CRP levels was observed after CPAP therapy (0·74 ± 0·62 mg dL^{-1} vs. 0·31 ± 0·29 mg dL^{-1}, $P < 0·001$) in the whole patient group. The evolution of CRP values showed a gradual decrease at 3 months with a steep decline at 6 months, reaching a plateau after this time point. When the patients were divided into those with good and poor compliance with CPAP therapy, the above CRP evolution pattern was observed only in the former group.

Conclusion Good CPAP compliance results in a significant CRP reduction. To achieve the best positive impact on cardiovascular morbidity and mortality, a time period of at least 6 months of CPAP use is required.

Keywords CPAP adherence, C-reactive protein, obstructive sleep apnoea.

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Introduction

Obstructive sleep apnoea (OSA) is characterized by repeated cessations of breathing during sleep, as a result of partial or complete pharyngeal collapse secondary to functional and anatomical factors [1]. OSA has been increasingly linked to cardiovascular and cerebrovascular morbidity and mortality and this association makes OSA a serious, potentially life-threading condition [2,3]. The pathogenesis of cardiovascular complications in OSA is multifactorial and not entirely understood, involving several mechanisms, such as sympathetic activation, endothelial dysfunction and metabolic dysregulation. There is growing evidence that the underlying inflammatory process leading to endothelial dysfunction plays a crucial role in the progression of atherosclerosis [4–9].

One of the proposed links between OSA and inflammation is C-reactive protein (CRP). This acute phase protein is directly implicated in atherogenesis, because it promotes the secretion of inflammatory mediators by the vascular endothelium and opsonizes low-density lipoprotein for uptake by macrophages in atherosclerotic plaques [10,11]. CRP levels are recognized as potent predictors of future cardiovascular events; however, elevated levels may be influenced by the presence of confounding factors, particularly obesity [12,13]. Most of the published studies so far [14–16] showed increased CRP levels in OSA patients, even though the role of adiposity and/or sleep duration in the observed CRP elevation in OSA patients has been questioned by others [17,18].

Effective treatment with continuous positive airway pressure (CPAP) is associated with a significant decrease of inflammatory markers. This evidence is particularly strong for tumour necrosis factor (TNF)-alpha, whereas studies on interleukin (IL)-6 and CRP have yielded conflicting results, possibly because of the confounding effects of adiposity [4,9,19,20].

[1]These authors had the same contribution in this work.

Yokoe *et al.* [19] and Steiropoulos *et al.* [21] reported that 1 and 6 months of CPAP therapy, respectively, decreased CRP and IL-6 levels in patients with OSA. In contrast, Akashiba *et al.* [20] reported that > 6 months of CPAP therapy did not decrease CRP levels in patients with OSA. Whether short-term or long-term CPAP therapy decreases CRP levels in patients with OSA is still controversial, and adherence to CPAP therapy may be an important determinant [21–23].

None of the above-mentioned studies have described the time course of a CRP decrease after CPAP therapy, whereas the patients' follow-up period was relatively short, ranging from 1 to 6 months. Additionally, the number of patients included was small.

Therefore, our study aimed to investigate the impact of CPAP therapy on CRP levels, in a large cohort of patients with moderate to severe OSA free of medical comorbitities, followed for up to 1 year. The evolution of CRP was assessed before CPAP initiation and after 3, 6, and 12 months of therapy. As a significant proportion of our patients showed poor CPAP compliance on a long-term basis, we also assessed whether adequate CPAP use impacts differently on CRP levels.

Materials and methods

Patients

We performed a prospective study on consecutive subjects, not previously treated for OSA, recruited from the Sleep Disorders Unit, University Hospital of Heraklion, Crete, for evaluation of OSA. Subjects were seeking treatment for OSA-suggestive symptoms, such as excessive daytime sleepiness and/or drowsy driving, snoring, choking during sleep and disruptive sleep. All subjects provided written informed consent and ethical approval was provided by the University Hospital's Ethics Committee.

Following enrollment, subjects underwent a detailed evaluation that included a clinical history focused on sleep-related symptoms, associated conditions and comorbidities, and a physical examination. Additionally, smoking was quantified during the initial interview. The degree of diurnal somnolence was determined using the Greek version of the Epworth sleepiness scale [24]. Anthropometric variables, such as age, height, weight, neck, waist and hip circumference were also recorded.

All subjects underwent attended overnight polysomnography (PSG) to identify possible underlying OSA. Exclusion criteria were: chronic obstructive pulmonary disease, diabetes mellitus, coronary artery disease, congestive heart failure or polysomnographic features suggestive of central sleep apnoea syndromes, chronic renal failure, known dyslipidemia, hypothyroidism, smoking history, chronic or recent clinically infectious or inflammatory condition, morbid obesity and recent use of anti-inflammatory or antibiotic drugs. None of the patients was receiving statin therapy.

Patients with moderate to severe OSA who initially accepted CPAP treatment underwent a second sleep study for CPAP titration to determine the effective CPAP level (CPAPeff) within 1 week of the first diagnostic polysomnography. Patients were wired up for full polysomnography and then CPAP was manually titrated to the correct therapeutic pressure to abolish all 'visible' nocturnal OSA events. They were asked to use the CPAP machine for at least 4 h per night.

Before the initiation of CPAP therapy, blood was collected between 8:00 and 9:00 AM, following an overnight fast, for the measurement of serum levels of high sensitivity (hs)-CRP.

Follow-up and compliance assessment

Patients under CPAP treatment were followed up by our CPAP-clinic monthly, independently of CPAP use. The hours per day and percentage of days that CPAP was used were monitored (IC card; Respironics, Inc., Murrysville, PA, USA) at the monthly clinical assessment. We divided the patients into two groups based on CPAP usage. Patients using CPAP > 4 h day^{-1} and > 5 days per week were designated as the good compliance group, while those with CPAP use < 4 h day^{-1}, < 5 days per week were considered the poor compliance group (Fig. 1). At the 3rd, 6th and 12th month of CPAP use a follow-up examination, the same as at baseline, was performed and blood samples were again collected from the patients.

Polysomnography

Overnight attended polysomnography (Alice 5, Respironics) was performed in our sleep disorders unit. Patients underwent a full diagnostic PSG study, according to standard techniques, with monitoring of the electroencephalogram (EEG) using frontal, central and occipital leads, electro-oculogram (EOG), electromyogram (EMG), flow (by oronasal thermistor and nasal air pressure transducer), thoracic and abdominal respiratory effort by uncalibrated impedance plethysmography belts, oximetry, and body position. Snoring was recorded by a microphone placed on the anterior neck. A single modified type II EKG lead was used for cardiac monitoring.

Polysomnographic recordings were manually interpreted over 30-s periods, in accordance with the guidelines of Rechtschaffen and Kales and the new AASM guidelines [25,26], and the scorer was blinded to the PSG findings of the first assessment. The determination of sleep stages and arousals was performed according to the AASM 2007 criteria and by using EEG montages including frontal, central and occipital leads [26].

Blood collection and analysis

Venous blood was collected in all subjects for baseline hs-CRP measurements between 8:00 and 9:00 AM, following an

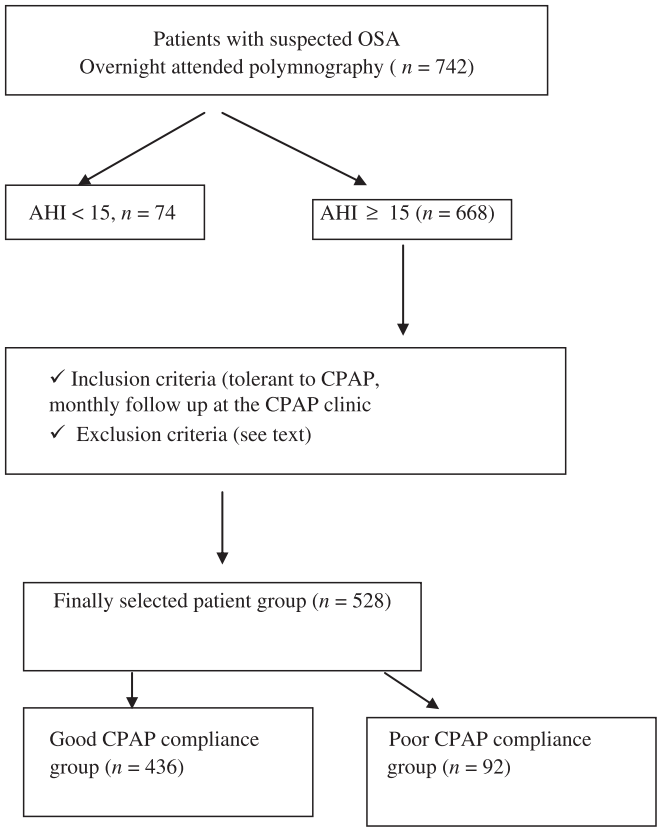

Figure 1 Flowchart of patient recruitment.

overnight fast, shortly after the conclusion of the overnight sleep recordings. At the 3rd, 6th and 12th month of CPAP use blood samples were drawn again for hs-CRP measurements in both groups. All venous samples were centrifuged and serum was separated into multiple aliquots and stored at −80 °C until assay. CRP levels were measured by means of particle-enhanced immunonephelometry using BN Systems (Dade Behring Inc.; Newark, NJ, USA). The lower CRP detection limit was 0·01 mg dL^{-1}.

Statistical analysis

Results are presented as means ± SD. The Kolmogorov–Smirnov test was used to confirm normality. Differences between consecutive CRP values were assessed by a one-way analysis of variance (ANOVA) test with the Bonferroni correction. CRP concentrations before and 1 year after CPAP therapy were assessed by the paired *t*-test. Demographic and polysomnographic data were compared between the good and poor CPAP compliance groups using the unpaired *t*-test (normally distributed data) or Mann–Whitney *U*-test (not normally distributed data). Correlations between CRP values and sleep disorder breathing parameters (apnoea–hypopnea index, arousal index, oxygen desaturation index, mean oxygen saturation during sleep and lowest oxygen saturation during sleep) were assessed by the Spearman correlation (not normally distributed data). We analysed the association between AHI and CRP levels with univariate analysis, without any adjustment for confounding variables to detect any possible relations. We then used multiple linear regression to identify the variables that made an important contribution to the variability of CRP levels and to adjust for all confounding variables with analysis of covariance. The percentage change of CRP values from baseline at 3, 6 and 12 months was calculated as (pre–post/pre) × 100. Statistical analysis was performed using SPSS 16 for Windows, Chicago, IL, USA. The significance criterion was defined at a P level < 0·05.

Results

We prospectively evaluated 742 patients (463 males and 279 females) with suspected OSA referred to our Sleep Disorders Unit. Of those, 74 were excluded as their apnoea–hypopnea index (AHI) was either within normal limits, or consistent with mild SDB (AHI < 15 per h sleep). Of the remaining 668 patients, 101 were excluded based on the above-mentioned exclusion criteria. Thirty-nine of the 567 initially recruited were withdrawn from the study. Twenty of them presented a change in Body Mass Index (BMI) of > 5% at baseline and 19 did not follow the scheduled re-examinations (Fig. 1). The baseline demographic and polysomnographic data of the remaining 528 patients (304 males and 224 females) are shown in Table 1. An interesting feature is the number of included females (ratio male/female 1·4/1), compared with previous studies. Although it should be mentioned that the initial 742 patient group had a higher male/female ration (1·7/1) that decreased after patient exclusion (flowchart Fig. 1) as more males compared with females did not fulfil the study inclusion criteria. By comparison of the above data between the good and poor compliance group, we found that patients in the good compliance group were heavier, sleepier and with a more severe spectrum of disease severity (Table 1).

Statistically significant correlations were noted between CRP values and AHI (P < 0·0001, rho = 0·54), arousal index (P < 0·0001, rho = 0·39), oxygen desaturation index (P < 0·0001, rho = 0·52), mean oxygen saturation during sleep (P < 0·0001, rho = −0·48) and lowest oxygen saturation during sleep (P < 0·0001, rho = −0·53) (Fig. 2a–c). We performed multiple linear regression for the whole patient group (n = 528), assigning CRP as the dependent variable and gender, age, BMI, and AHI as independent predictors found from previous univariate analyses. The variables contributed significantly to the model (r = 0·485, P = 0·0001). Table 2 shows that the

Table 1 Demographic and polysomnographic data (whole patient group, good and poor CPAP compliance groups)

	Total patients (n = 528)	Good compliance group (n = 436)	Poor compliance group(n = 92)	P-value (good vs. poor compliance group)
Age (years)	47·6 ± 12·3	53·2 ± 11·7	43 ± 13·1	< 0·0001
Gender (male/female)	304/224	252/184	52/40	
BMI (kg m^{-2})	32·7 ± 6·3	35·3 ± 7·1	30·1 ± 5·6	< 0·001
ESS score	14·3 ± 4·6	17·1 ± 4·7	11·6 ± 4·5	< 0·0001
AHI (events h^{-1})	35·2 ± 18·9	43·3 ± 23·9	27·2 ± 13·9	< 0·0001
Arousal index (arousals h^{-1})	30·3 ± 11·9	38 ± 14·7	22·7 ± 9·1	< 0·0001
Oxygen desaturation index	32·3 ± 20·2	47·3 ± 28·3	17·4 ± 13·1	< 0·0001
Lowest SaO_2 (%)	81·3 ± 7·2	75·9 ± 9·6	86·8 ± 4·8	< 0·0001
Mean SaO_2 (%)	90·3 ± 4·1	87·8 ± 5	92·8 ± 3·2	< 0·0001
Arterial pressure				
Systolic (mm Hg)	122·4 ± 16·1	124·5 ± 17·2	120·1 ± 13·7	0·09
Diastolic (mmHg)	75·5 ± 11·4	76·1 ± 12	74·3 ± 9·4	0·44
Glucose (mg dL^{-1})	92·1 ± 15·3	93·4 ± 14·7	90·8 ± 16·2	0·97
Cholesterol (mg dL^{-1})	208·1 ± 36·4	213 ± 34·7	196·5 ± 40·8	0·19
Triglyceride (mg dL^{-1})	106·7 ± 34·5	112 ± 31·1	104·1 ± 36·9	0·58
LDL (mg dL^{-1})	139·2 ± 32·6	140 ± 30·8	138·6 ± 34·8	0·98
HDL (mg dL^{-1})	51·7 ± 13·5	50·1 ± 12·8	56·4 ± 17·6	0·24

Values are given as mean ± SD, unless otherwise indicated.
BMI, body mass index; ESS, Epworth Sleepiness Scale; AHI, apnoea-hypopnea index; SaO_2, pulse oximetry saturation; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

apnoea–hypopnea index (AHI) was significantly related to CRP levels after adjustment for age and BMI.

In the whole patient population included (528 patients), a significant reduction was found in CRP levels after CPAP therapy (0·74 ± 0·62 mg dL^{-1} before CPAP therapy vs. 0·31 ± 0·29 mg dL^{-1} after 1 year of CPAP therapy, $P < 0·001$, Fig. 3a). The evolution of CRP values during the 1 year of follow-up showed a gradual decrease at 3 months (10·8%), with a steep decline at 6 months (56·6%), reaching a plateau after that time (2·8% decrease) (Fig. 3b). When the study sample was divided into two groups according to the compliance with CPAP therapy (good and poor CPAP compliance groups), the statistically significant reduction in CRP was found only in the good compliance group (0·79 ± 0·66 mg dL^{-1} before CPAP treatment vs. 0·29 ± 0·32 mg dL^{-1} at 1 year follow-up, $P < 0·001$, Fig. 4a,b). On the other hand, there was no statistically significant decrease in consecutive assessments of CRP in the poor CPAP compliance group (Fig. 5a,b), although there was a trend to significance in the difference between initial CRP values and those after 1 year CPAP therapy (0·45 ± 0·28 mg dL^{-1} vs. 0·38 ± 0·26 mg dL^{-1}, $P = 0·06$).

Eighty-two of the included subjects had a normal CRP level (< 0·25 mg dL^{-1}) before CPAP therapy (66 with good CPAP and 16 with poor CPAP compliance). The decrease in CRP levels in these 82 patients showed no statistically significant differences (initial: 0·08 ± 0·07 mg dL^{-1}, 3 months: 0·07 ± 0·07 mg dL^{-1}, 6 months: 0·06 ± 0·1 mg dL^{-1}, 1 year: 0·05 ± 0·04 mg dL^{-1}, $P > 0·05$). However, a result differentiation was noted when CPAP adherence was taken into account. More specifically, the good compliance group showed a gradual initial decrease of CRP values at 3 months (11·8%), with a steep decline at 6 months (61·9%) and appearance of a plateau (2·3%) after that time of follow-up (Fig. 6). In contrast, no statistically significant CRP decrease was observed in the poor CPAP compliance group during the follow-up period (initial: 0·13 ± 0·09 mg dL^{-1}, 3 months: 0·12 ± 0·08 mg dL^{-1}, 6 months: 0·16 ± 0·2 mg dL^{-1}, 1 year: 0·10 ± 0·07 mg dL^{-1}, $P > 0·05$).

Discussion

This is the first study to investigate the evolution of CRP during a 1-year follow-up period in a large cohort of otherwise healthy

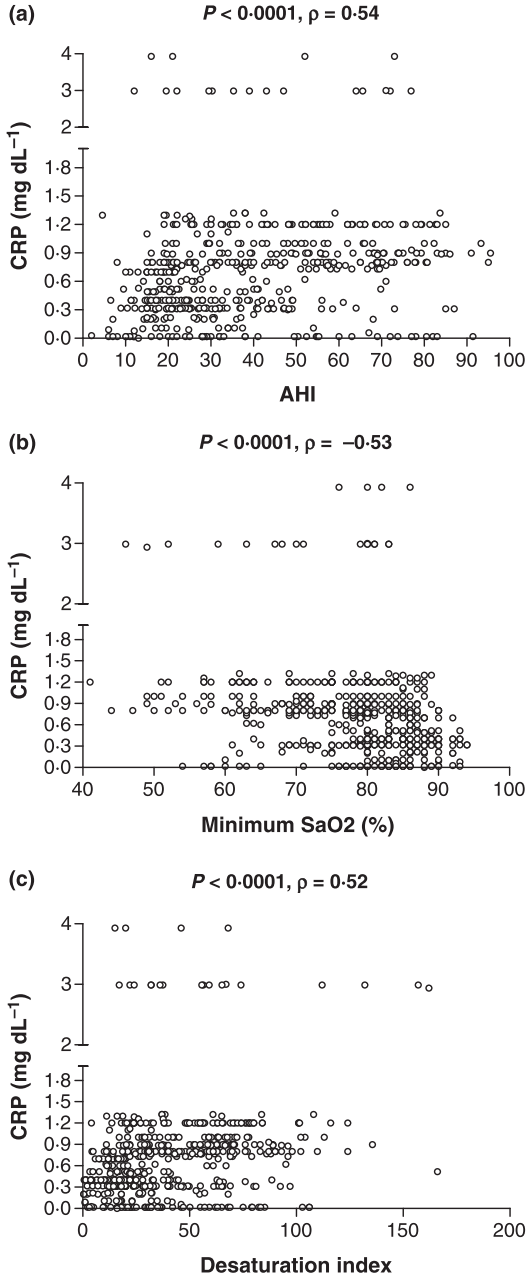

Figure 2 Correlation between CRP values and OSA parameters. (a) Correlation between CRP values and AHI, (b) correlation between CRP values and minimum nocturnal SaO_2 (%) and (c) correlation between CRP values and oxygen desaturation index (events/hour of sleep).

Table 2 Multiple linear regression analysis for CRP levels as dependent variable and age, BMI and AHI index as predictors

Variables	B	SE	*t*	*P*
Age	0·112	0·001	3·437	0·001
BMI	0·210	0·003	5·945	0·0001
AHI	0·335	0·001	9·496	0·0001

BMI, body mass index; AHI, apnoea-hypopnea index; CRP, C-reactive protein.

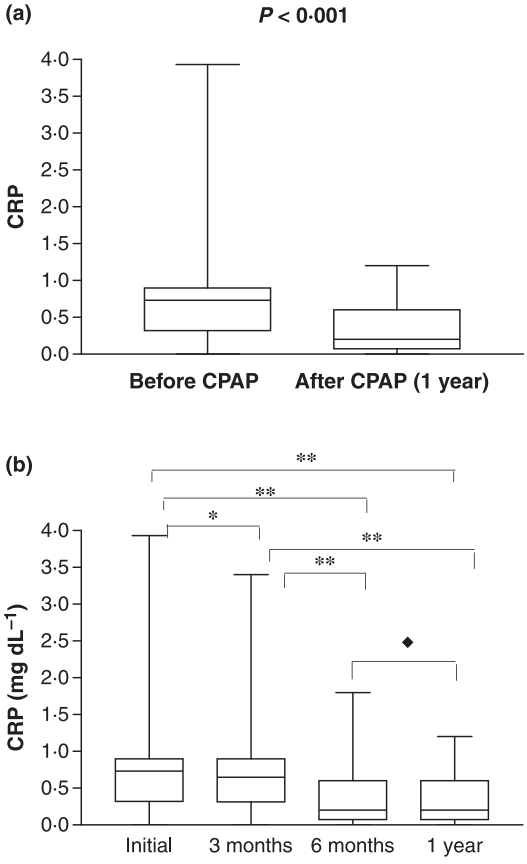

Figure 3 Whole OSA patient group. (a) Box plot showing CRP values before and 1 year after CPAP therapy. (b) Evolution of CRP values during the 1-year follow-up. Middle horizontal line inside box indicates median. Bottom and top of the box are 25th and 75th percentiles, and the error bars outside the box represent maximum and minimum values, respectively. *$P < 0·05$, **$P < 0·001$, ♦NS (non-significant, $P > 0·05$).

patients with moderate to severe OSA under CPAP treatment. CRP evolution patterns were assessed, not only in the whole patient group, but also in relation to the observed adherence to CPAP therapy. CRP values showed a significant decrease between the first measurements during CPAP initiation and those at the 3rd and 6th month of the follow-up period. An interesting feature was the fact that CRP levels continued to decrease for a period to up to 6 months, whereas after this time point they showed a plateau response despite continued CPAP

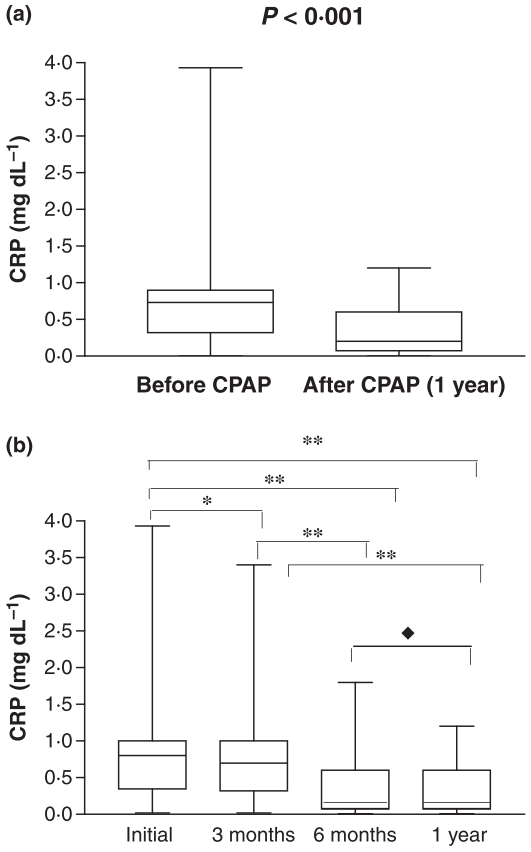

Figure 4 Good CPAP compliance group. (a) Box plot showing CRP values before and 1 year after CPAP therapy. (b) Evolution of CRP values during the 1-year follow-up. Middle horizontal line inside box indicates median. Bottom and top of the box are 25th and 75th percentiles, and the error bars outside the box represent maximum and minimum values, respectively. *$P < 0{\cdot}05$, **$P < 0{\cdot}001$, ♦NS (non-significant, $P > 0{\cdot}05$).

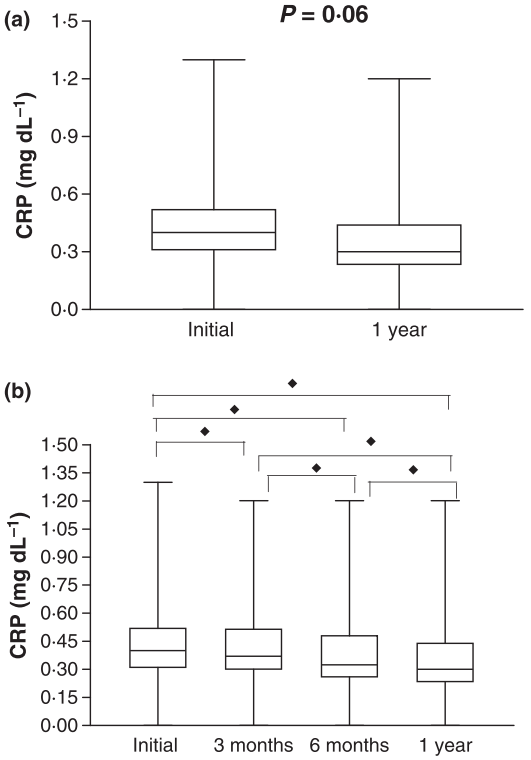

Figure 5 Poor CPAP compliance group. (a) Box plot showing CRP values before and 1 year after CPAP therapy. (b) Evolution of CRP values during the 1-year follow-up. Middle horizontal line inside box indicates median. Bottom and top of the box are 25th and 75th percentiles, and the error bars outside the box represent maximum and minimum values, respectively. ♦NS (non-significant, $P > 0{\cdot}05$).

use. Such an evolution pattern indicates that the therapeutic effects of CPAP treatment on the well known OSA-related cardiovascular risk factors require a minimum CPAP use of 6 months. The potential role of CRP in the pathogenesis of cardiovascular complications in OSA is crucial, although the whole inflammatory process is multifactorial, involving several other mechanisms and inflammatory markers, such as IL-6 or TNF-a. Whether these markers show a similar time course behaviour to CRP after CPAP application is an interesting although unresolved issue that should be addressed prospectively.

The observed CRP evolution showed significant differences after the patients were divided into a good and a poor CPAP compliance group. The statistically significant decrease, and the above-mentioned plateau effect after the 6th month of therapy, was found only in patients with good CPAP compliance. CRP also decreased in poor CPAP users, although only a statistically

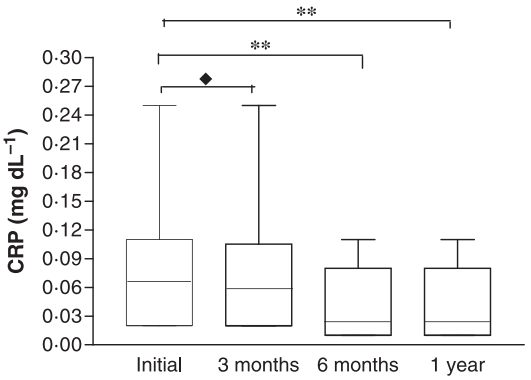

Figure 6 Evolution of CRP values during the 1-year follow-up in patients of the good CPAP compliance group who had normal CRP levels before CPAP initiation. Middle horizontal line inside box indicates median. Bottom and top of the box are 25th and 75th percentiles. **$P < 0{\cdot}001$, ♦NS (non-significant, $P > 0{\cdot}05$).

significant trend was achieved after 1 year of therapy. Based on that observation, it seems that if CPAP use is inadequate based on generally accepted criteria (use < 4 h per night and < 5 days per week) there is a limited influence on OSA-related cardiovascular complications. Once again, CRP is only a part in the complex inflammatory process characterizing OSA and the assessment of the evolution of other markers is important to draw final conclusions.

Our results agree with those of Yokoe *et al*. [19] as well as with Steiropoulos *et al*. [21]. In those studies, 1–6 months' CPAP therapy was associated with a significant decrease in CRP values. The statistical power of our study compared with the above is superior, not only due to the large number of patients included, but also by the use of multiple time points during the CRP evolution assessment. We can confidently rely on the statistical law stating that random errors average out when the evolution of a parameter is assessed in large samples and during multiple time points [23]. We opted to use the initial and three follow-up points to precisely determine the rate of change of CRP values over time, which was a 9·4% decrease per month for the group as a whole and a 10·3% decrease per month for the good compliance group.

The poor and good CPAP compliance groups were separated according to the monthly CPAP use based on monitoring the CPAP device memory card at the monthly check ups. Significant differences were observed when these groups were compared. The good CPAP users were more sleepy (based on the Epworth sleepiness scale score), had more severe OSA and were heavier and older compared with the poor CPAP users. The variable adherence to CPAP treatment has been always recognized as one of the most important limitations of this therapy. Our poor CPAP compliance group population with the above characteristics shows similarities to other previously described patients with inadequate CPAP adherence [18]. The CRP evolution pattern of our poor CPAP users showed a limited CRP decrease, probably not adequate to eliminate the potential inflammation-related cardiovascular risk. Further studies are necessary to find methods to increase CPAP acceptance in such OSA patients.

Our study results showed a significant reduction of CRP levels not only in patients with initially high CRP ($\geq$ 0·2 mg dL^{-1}) but also in patients with normal CRP levels, provided that CPAP compliance was achieved. This is in contrast to the recently reported data by Ishida *et al*. [22], although the small number of subjects included in that study and ethnic–racial differences (the study included only Japanese patients) probably influenced the reported results, at least in OSA patients with normal CRP values before the start of CPAP therapy. The interesting finding in the good CPAP compliance patient group with normal CRP values compared to those with increased CRP was the evolution of CRP values, which showed a significant decrease only after the 3rd month of CPAP therapy, and not earlier as in the latter group. The plateau response after 6 months of CPAP therapy was the same in both groups, irrespective of whether CRP values were within or outside the normal range during CPAP initiation.

In agreement with previous studies [14–16], sleep disordered breathing (SDB) was associated with elevated levels of CRP, independently of age, BMI, waist and neck circumference. A dose–response relationship was identified between serum CRP levels, the frequency of disordered breathing events, the arousal index (AI) and the degree of nocturnal hypoxemia. The main confounding factor in the relation between CRP and SDB, namely BMI, remained relatively stable in our patient group, without statistically significant differences during the follow-up period. Additionally, our patient population was free of any medical comorbitities that might have influenced the CRP values and their evolution during the studied period.

Our data related to CRP, one of the most important inflammatory factors, provide strong evidence of a causal relationship between OSA and low grade inflammation. Although the underlying mechanisms of such causality are not known, there are data suggesting that intermittent hypoxia may be a key factor in the low grade systemic inflammation process in OSA patients [6,7]. Hypoxic exposure stimulates the expression and production of IL-6, the principal initiator of the hepatic acute phase response. Moreover, experimental data show that alterations in sleep duration and architecture can elevate CRP levels and trigger the atherogenic process. As already mentioned, in this study, there was a dose–response relationship between CRP levels and AHI, mean and lowest SaO_2 and with the severity of sleep architecture impairment as reflected by the arousal index.

A limitation of our study was the fact that obesity was assessed only by indirect measurements such as body mass index (BMI), waist, hip and neck circumference. It is well known that obesity remains the main confounding factor related to the influence of CPAP on the metabolic status of OSA [27,28]; therefore, the use of methods that directly measure total body fat, such as dual energy X-ray absorpiometry (DXA scanning) [29] and MRI or CT for visceral fat accumulation, will be essential to clarify whether the observed associations between OSA and CRP persist after accounting for such measures. However, the BMI of our studied group remained, based on the strict exclusion criteria used, unchanged during the study period. Thus, we eliminated as far as possible any influence of obesity on CRP values. Another limitation of our study is related to the selected population including patients free of medical co morbidities that might influence the assessed CRP levels. This probably decreases the generalization of our features and indicates the need for further research on this topic including OSA patients irrespective of the existence of other comorbidities.

In conclusion, good CPAP compliance results in a significant CRP reduction. To achieve the best positive impact on potential cardiovascular morbidity and mortality, at least in relation to the CRP related inflammatory process, a time period of at least 6 months of CPAP use is required.

Address
Sleep Disorders Unit, Department of Thoracic Medicine, Medical School, University of Crete, 71110 Heraklion Crete, Greece (S. E. Schiza, I. Bouloukaki, E. Kallergis, N. Tzanakis, E. Tzortzaki, E. Vlachaki, N. M. Siafakas); Sleep Disorders Center, Pulmonary Department, 401 General Army Hospital, Athens, Greece (C. Mermigkis, P. Panagiotis).
Correspondence to: Sophia E. Schiza, MD, PhD, Assistant Professor of Thoracic Medicine, Medical School, University of Crete, 71110 Heraklion Crete, Greece. Tel.: 00 30 281 039 2433; fax: 00 30 281 039 4670; e-mail: schiza@med.uoc.gr

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References

1 Patil SP, Schneider H, Schwartz AR, Smith PL. Adult obstructive sleep apnea: pathophysiology and diagnosis. *Chest* 2007;**132**:325–37.
2 Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;**342**:1378–84.
3 Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F *et al*. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;**163**:19–25.
4 Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;**105**:1135–43.
5 Somers VK, White DP, Amin R, Abraham W, Costa F, Culebras A. Sleep apnea and Cardiovascular disease: an American Heart Association/American College of Cardiology foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke council and Council of Cardiovascular Nursing. *J Am Coll Cardiol* 2008;**52**:686–717.
6 Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? *Thorax* 2009;**64**:631–6.
7 Lévy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J* 2009;**34**:243–60.
8 Minoguchi K, Yokoe T, Tanaka A, Ohta S, Hirano T, Yoshino G *et al*. Association between lipid peroxidation and inflammation in obstructive sleep apnoea. *Eur Respir J* 2006;**28**:378–85.
9 Steiropoulos P, Kotsianidis I, Nena E, Tsara V, Gounari E, Hatzizisi O *et al*. Long term effect of continuous positive airway pressure therapy on inflammation markers of patients with obstructive sleep apnea syndrome. *Sleep* 2009;**32**(4):537–43.
10 Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* 2001;**103**:1813–8.
11 Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;**347**:1557–65.
12 Heeschen C, Hamm CW, Bruemmer J, Simoons M. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators. Chimeric C7E3 Anti Platelet Therapy in Unstable Angina Refractory to standard treatment trial. *J Am Coll Cardiol* 2000;**35**:1535–42.
13 Cao JJ, Arnold AM, Manolio TA, Polak J, Psaty B, Hirsch C *et al*. Association of carotid artery intima-media thickness, plaques and C-reactive protein with future cardiovascular disease and all cause mortality: the Cardiovascular Health Study. *Circulation* 2007;**116**:32–8.
14 Shamsuzzaman ASM, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V *et al*. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation* 2002;**105**:2462–4.
15 Kokturk O, Ciftci TU, Mollarecep E, Ciftci B. Elevated C-reactive protein levels and increased cardiovascular risk in patients with obstructive sleep apnea syndrome. *Int Heart J* 2005;**46**:801–9.
16 Punjabi NM, Beamer BA. C-reactive protein is associated with sleep disordered breathing independent of adiposity. *Sleep* 2007;**30**:29–34.
17 Guilleminault C, Kirisoglu C, Ohayon MM. C-reactive protein and sleep-disordered breathing. *Sleep* 2004;**27**:1507–11.
18 Weaver T, Grunstein R. Adherence to continuous positive airway pressure therapy. The challenge to effective treatment. *Proc Am Thorac Soc* 2008;**5**:173–8.
19 Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G. Elevated levels of C-reactive protein and Interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* 2003;**107**:1129–34.
20 Akashiba T, Akahoshi T, Kawahara S, Majima T, Horie T. Effects of long-term nasal continuous positive airway pressure on C-reactive protein in patients with obstructive sleep apnea syndrome. *Intern Med* 2005;**44**:899–900.
21 Steiropoulos P, Tsara V, Nena F, Fitili C, Kataropoulou M, Froudarakis M *et al*. Effect of continuous positive airway pressure treatment on serum cardiovascular risk factors in patients with obstructive sleep apnea hypopnea syndrome. *Chest* 2007;**132**:843–51.
22 Ishida K, Kato M, Kato Y, Yanagihara K, Kinugasa Y, Kotani K *et al*. Appropriate use of nasal continuous positive airway pressure decreases elevated C-reactive protein in patients with obstructive sleep apnea. *Chest* 2009;**136**:125–9.
23 Torres JP, Casanova C, Celli BR. Sex, forced expiratory volume in 1s decline, body weight change and C-reactive protein in COPD pts. *Eur Respir J* 2009;**34**:776.
24 Tsara V, Serasli E, Amfilochiou A, Constantinidis T, Christaki P. Greek version of the Epworth Sleepiness Scale. *Sleep Breath* 2004;**8**:91–5.
25 Rechtschaffen A, Kales A, eds. *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects*. BIS/BRI University of California, Los Angeles; 1968.
26 Iber K, Ancoli-Israel S, Chesson AL, Quan SF. *The AASM Manual for the Scoring of Sleep and Associated Events*. Westchester, IL: American Academy of Sleep Medicine; 2007.
27 Steiropoulos P, Papanas N, Maltezos E, Bouros D. Is there a metabolic effect of continuous positive airway pressure in sleep apnoea? Adherence should not be underestimated. *Eur Respir J* 2009;**34**:1209–10.
28 Lévy P. From the author: *Eur Respir J* 2009;**34**:1210–1.
29 Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone mineral and soft tissue composition. *Am J Clin Nutr* 1990;**51**:1106–12.