

## ORIGINAL ARTICLE

# CPAP Does Not Reduce Inflammatory Biomarkers in Patients With Coronary Artery Disease and Nonsleepy Obstructive Sleep Apnea: A Randomized Controlled Trial

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**Objectives:** Obstructive sleep apnea (OSA) and enhanced vascular inflammation coexist in patients with coronary artery disease (CAD). Continuous positive airway pressure (CPAP) is first-line treatment for OSA with daytime sleepiness. This analysis of data from the RICCADSA (Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea) trial investigated the effects of CPAP on inflammatory markers in patients with CAD and nonsleepy OSA.

**Methods:** This single-center, randomized, controlled, open-label trial enrolled consecutive revascularized patients with nonsleepy OSA (apnea–hypopnea index >15/h; Epworth Sleepiness Scale score <10). Levels of high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, IL-8, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were measured in blood samples taken at baseline (median 94 days after revascularization) and after 1 year of follow-up in patients randomized to CPAP or no-CPAP.

**Results:** A total of 220 patients with analyzable blood samples at baseline and 1 year were included. Baseline IL-6 levels were significantly lower in the CPAP versus no-CPAP group (median 3.1 pmol/L [interquartile range 1.3–5.7] vs. 4.2 pmol/L [2.0–8.9], respectively;  $p = .005$ ). At 1-year follow-up, median IL-6 levels were significantly reduced in both groups (to 2.2 pmol/L [1.2–3.9] in the CPAP group and to 2.2 [1.2–4.7] in no-CPAP group; both  $p < .001$  vs. baseline). IL-8, hs-CRP, and TNF- $\alpha$  did not change significantly from baseline. There was no association between CPAP adherence and changes in inflammatory marker levels.

**Conclusions:** In patients with stable CAD and nonsleepy OSA, inflammatory biomarkers did not change significantly over time except for IL-6 levels, which reduced to the same extent in the CPAP and no-CPAP groups.

**Clinical Trial Registration:** [ClinicalTrials.gov](https://clinicaltrials.gov), ID: NCT00519597; [researchweb.org](https://researchweb.org), VGSKAS-4731.

**Keywords:** continuous positive airway pressure, coronary artery disease, obstructive sleep apnea, interleukin-6, interleukin-8, tumor necrosis factor- $\alpha$ .

## Statement of Significance

Coronary artery disease (CAD) and obstructive sleep apnea (OSA) are associated with systemic inflammation. However, data on the effects of treating OSA on inflammatory biomarkers are inconsistent. This study was the first large, randomized, controlled clinical trial to investigate the effects of continuous positive airway pressure (CPAP) on inflammatory markers after revascularization in CAD patients with nonsleepy OSA. After 1 year, the only biomarker significantly reduced compared with baseline was IL-6, which decreased to a similar level in the CPAP and no-CPAP groups. This probably represents the natural course of IL-6 after revascularization rather than any effect of treatment. Additional studies are needed to better define the effects of CPAP on inflammatory markers in CAD patients with OSA.

## INTRODUCTION

Increased inflammatory activity plays an important role in the development of atherosclerotic plaques.<sup>1</sup> In addition, blood levels of inflammatory markers are predictors of future cardiovascular events, both in the general population<sup>2,3</sup> and in individuals with known cardiovascular disease.<sup>4</sup> The most studied biomarker in this context is high-sensitivity C-reactive protein (hs-CRP).<sup>4,5</sup> However, elevated levels of both interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$  have also been associated with an increased risk of cardiovascular events.<sup>3,6,7</sup> The suggested pathophysiological mechanism underlying this association is low-grade inflammation in atherosclerotic plaques located in vascular beds, which could release inflammatory cytokines (eg, IL-6 and TNF- $\alpha$ ) and thereby trigger an inflammatory cascade, including low-grade production of hs-CRP in the liver.<sup>1</sup> Conversely, high levels of CRP indicate a more rapid inflammatory process, such as an acute infection, rather than mirroring the typical low-grade inflammation of an atherosclerotic plaque. A subtle increase in hs-CRP levels can be used in clinical settings as a complementary marker when measuring lipid levels in order to validate increased cardiovascular risk before initiation of statin treatment.<sup>8</sup>

Patients with obstructive sleep apnea (OSA) have been reported to show low-grade inflammatory activity.<sup>9</sup> This association probably has a number of underlying pathophysiological mechanisms, including the possibility that intermittent hypoxia and oxidative stress result in increased concentrations of free radicals, causing inflammation.<sup>10</sup> Hs-CRP, TNF- $\alpha$ , and IL-6 have all been shown to be elevated in patients with OSA.<sup>11</sup> Most studies investigating the link between OSA and inflammatory markers have been done on subjects recruited from a sleep clinic cohort. Little is known about the OSA–inflammation link in other populations. Data from the RICCADSA (Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea) study showed that patients with coronary artery disease (CAD) and OSA who had undergone revascularization have higher inflammatory marker levels than those with CAD only, independent of obesity.<sup>12</sup> Furthermore, intermittent hypoxemia appeared to be the factor most closely associated with the subtle increase in inflammatory markers.

In longitudinal studies, treatment of OSA with continuous positive airway pressure (CPAP) has been shown to decrease levels of circulating inflammatory markers, supporting a direct link between low-grade inflammation and OSA.<sup>13,14</sup> However,

it is uncertain whether individuals with nonsleepy OSA phenotype have the same decrease in inflammatory markers after CPAP treatment. . In a cohort study of patients with CAD and concomitant OSA, CPAP did lower inflammatory markers.<sup>15</sup> However, that study did not include a control group, thus a decrease in inflammatory markers in all patients after a cardiovascular event, irrespective of CPAP treatment, could not be excluded.

The current analysis of data from the RICCADSA trial<sup>12</sup> investigated the effects of CPAP on levels of inflammatory biomarkers in nonsleepy CAD patients with OSA.

## METHODS

### Study Design and Patients

The RICCADSA study was a single-center (two sites), open, randomized (1:1; CPAP/no-CPAP), parallel, interventional, superiority trial that investigated the long-term rate of adverse cardiovascular events in patients with CAD and nonsleepy OSA. The study design and population have been previously described in detail.<sup>12,16,17</sup> In brief, all consecutive patients with CAD ( $n = 1291$ ) who had recently (<6 months) undergone percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the Skaraborg County in West Sweden between September 29, 2005 and November 7, 2010 were invited to participate in the trial. The current analysis included patients in the randomized controlled trial (RCT) arm, who had blood samples suitable for analysis at baseline and 1-year follow-up (Figure 1). The observational arm was followed as additional control subjects for further post hoc comparisons of the sleepy versus nonsleepy phenotypes of CAD patients with concomitant OSA (to be reported separately), and not included in the current work.

The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Gothenburg (approval no. 207-05; 09.13.2005) and was conducted in accordance with the Declaration of Helsinki.<sup>18</sup> All patients signed a written informed consent form before the start of the study. The trial was registered with the national [researchweb.org](http://researchweb.org) (FoU i Sverige – Research and development in Sweden; nr VGSKAS-4731; 04.29.2005) and with [ClinicalTrials.gov](http://ClinicalTrials.gov) (NCT 00519597).

The random assignment of patients with CAD and nonsleepy OSA phenotype (apnea–hypopnea index [AHI]  $\geq 15$  events/h and Epworth Sleepiness Scale [ESS] score <10) was scheduled with a block size of eight patients (four CPAP and four controls in each block) stratified by gender and revascularization type (PCI/CABG).

### Comorbidities

Baseline anthropometric measurements, smoking habits, and medical histories of the entire study population were extracted from medical records transcribed at the time of mechanical revascularization. Body mass index (BMI) was calculated as body weight divided by height squared. Obesity was defined as a BMI  $\geq 30$  kg/m<sup>2</sup>.<sup>19</sup> Blood pressure (BP) was measured with a sphygmomanometer after  $\geq 15$  minutes' rest in the sitting position and using an appropriately sized arm-cuff. Data on known concomitant diseases at baseline, including hypertension and diabetes, the severity of CAD, angiographic findings, and type

of revascularization procedure (PCI or CABG) as well as medication use at baseline and during follow-up, were based on a combination of self-report and physician diagnosis, reported in patient records and national registers.

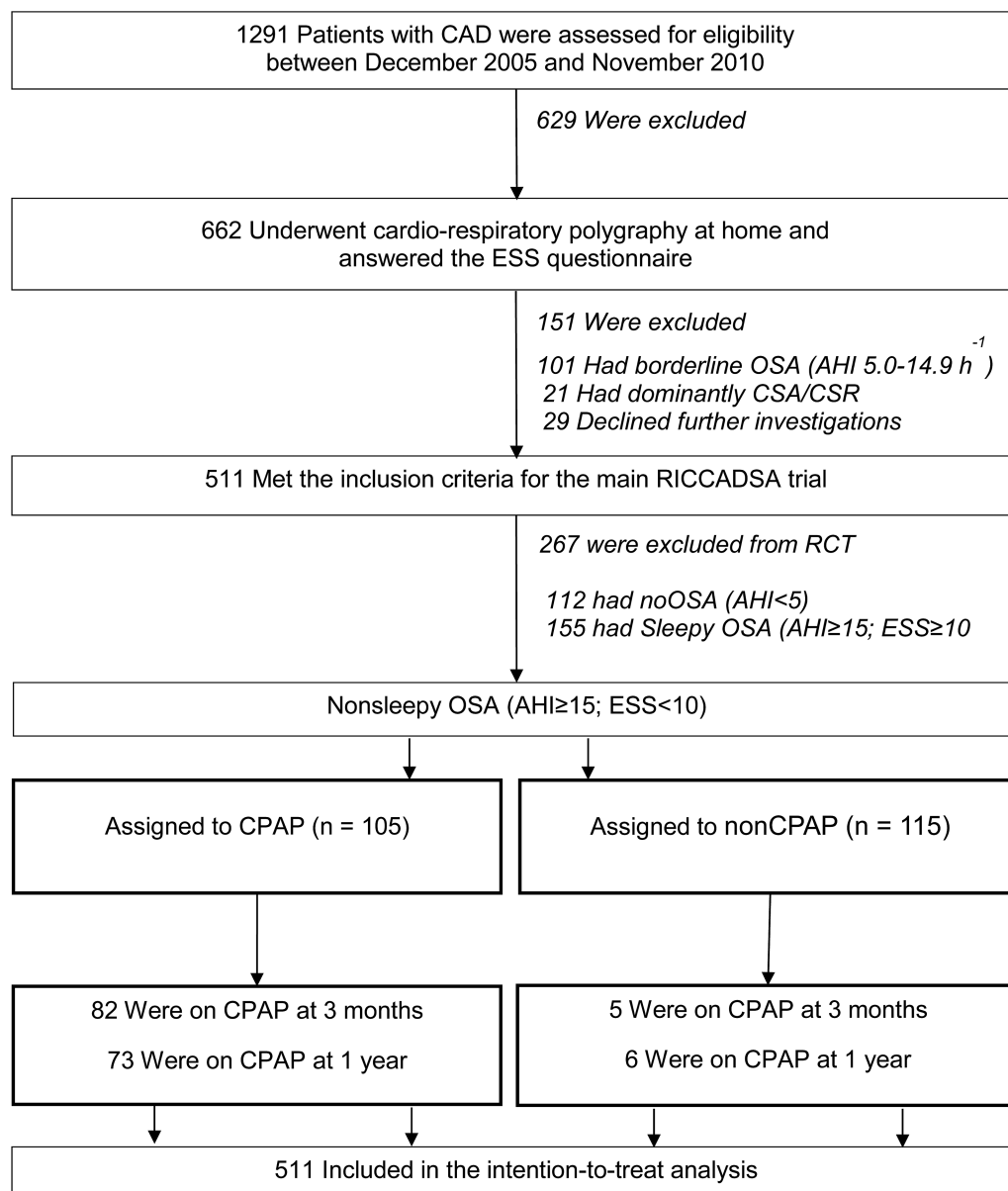
### Blood Sampling

After an overnight fast of at least 10 hours, all blood samples were collected using ethylenediaminetetraacetic acid and serum tubes in the morning (07:00–08.00 am) at the time of study inclusion and after baseline sleep recordings (median time since sleep study was 30 days [interquartile range (IQR) 21–45 days]; no differences between CPAP and no-CPAP subjects, and median time since coronary intervention was of 93 days [IQR 72–120 days], also without significant between-group differences). Blood samples were collected again after 3 and 12 months' follow-up. Tubes were centrifuged and plasma/serum samples were aliquoted and stored at  $-70^{\circ}\text{C}$ .

Serum levels of hs-CRP were measured by immunoturbidimetry using the infrared immunoassay rate method and the near-infrared particle immunoassay at the Karolinska University Laboratory (Solna, Sweden) in a routine clinical analyzer.<sup>20</sup> The detection limit for hs-CRP was 0.20 mg/L with a measuring range of 0.20–380 mg/L. Levels of the proinflammatory biomarkers IL-6, IL-8, and TNF- $\alpha$  were analyzed in undiluted plasma samples using commercially available MILLIPLEX MAP (based on Luminex technology) human serum adipokine assay kits in accordance with the manufacturer's instructions (Merck Millipore, MA, USA). Minimum detectable concentrations (assay sensitivities) for IL-6, IL-8, and TNF- $\alpha$  were 0.6, 0.2, and 0.14 pg/mL, respectively. IL-6, IL-8, and TNF- $\alpha$  concentrations in all samples (undiluted) were within the standard curve, ranging from 0 to 10 000 pg/mL. The intra-assay and inter-assay variabilities (generated from the mean of the percentage coefficient of variability from multiple reportable results across two different concentrations of analytes in one experiment or from two results each for two different concentrations of analytes across several different experiments) were 1.4%–7.9% and <21%, respectively.

### Sleep Recordings, Group Assignments, and Randomization

Details of the sleep recordings have been described previously.<sup>12,16</sup> In summary, the cardiorespiratory study included, at minimum, continuous recording from nasal cannulae, thoracic–abdominal motion, oxygen saturation, and body position. The patient's sleep time was estimated on the basis of self-reporting as well as the pattern of body movement during the study. Apnea was defined as an almost complete ( $\geq 90\%$ ) cessation of airflow, and hypopnea was defined as a reduction in thoracoabdominal movement of at least 50%, a reduction in nasal pressure amplitude of at least 50% for a minimum of 10 seconds, and reductions in both thoracoabdominal movement and nasal pressure amplitude.<sup>21</sup> In addition, the total number of significant oxyhemoglobin desaturations (defined as a decrease of at least 4% from the immediately preceding baseline value) was scored, and the oxygen desaturation index was calculated as the number of significant desaturations per hour of estimated sleep. Events with a reduction in thoracoabdominal movement of at least 30% with a reduction in nasal pressure amplitude of at least 30% for a minimum of 10



**Figure 1**—Study flow diagram. AHI, apnea–hypopnea index; CAD, coronary artery disease; CSA–CSR, central sleep apnea–Cheyne Stokes respiration; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; RICCADSA, Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea.

seconds or reductions in both thoracoabdominal movement and nasal pressure amplitude were also scored as hypopneas if there was significant oxygen desaturation ( $\geq 4\%$ ). OSA was defined as an AHI of at least 15 events/h of estimated sleep time.

### Interventions and Follow-up

OSA patients with nonsleepy OSA randomized to CPAP were informed about the technical procedure in the morning after polysomnography evaluation and equipped with an automatic (self-titrating) CPAP device (S8 or S9; ResMed, Sydney, Australia) with a nasal or full-face mask and humidifier by trained staff at the study center. All patients in the CPAP group were instructed to use CPAP at home for at least 4 hours every night, were contacted by telephone after 1 week, and followed up at

clinic visits after 1 month, 3 months, 6 months, 1 year, and yearly thereafter up to the end of the RICCADSA trial. Nonsleepy OSA patients who were randomized to the control (no CPAP) group and all patients who were overweight were advised about weight reduction, and followed up after 3, 6, and 12 months.

### CPAP Compliance

CPAP device data were checked at each scheduled follow-up visit, including settings and hours of CPAP use. CPAP pressure, mask leak, and residual AHI were also determined. All necessary adjustments of the CPAP device and mask fittings were done by sleep medicine unit staff according to standard clinical practice. Patients in the CPAP group who were unable to adhere to treatment were followed in the treatment arm, as defined in

the prespecified intention-to-treat (ITT) analysis. CPAP compliance at 12 months was based on CPAP hours/night adjusted for percentage of CPAP days per period (from the last previous visit to 1 year follow-up), and corresponding 4 hours of CPAP usage every night was defined as good compliance.

### Outcomes

The primary outcome for this analysis was the change in circulating levels of inflammatory biomarkers from baseline to 1 year; the change over time was compared in the CPAP and no-CPAP group. On-treatment analysis of changes from baseline in inflammatory markers was a secondary endpoint. Additional subgroup comparisons were conducted in obese versus non-obese patients as well as in minimally symptomatic versus asymptomatic patients based on the median ESS score as cutoff value in the current cohort.

### Statistical Analysis

Statistical analysis was performed using the IBM SPSS version 22.0 for Windows system (SPSS Inc., Chicago, IL, USA). Primary outcome data were analyzed on an ITT basis. For comparison between groups, independent sampled student *t*-test, or, when appropriate, Mann–Whitney *U*-test was used. Chi-square test or, when appropriate, Fisher’s exact test was used for comparison of categorical variables. Paired sampled student *t*-test was used for intraindividual comparisons of baseline and 12-month values. Results are given as median ± standard error of the mean (SEM), median (IQR) or mean ± SD, and categorical variables as numbers (percentages). All statistical tests were two-sided, and *p* values of <.05 were considered statistically significant.

## RESULTS

### Patient Population and Baseline Characteristics

A total of 511 revascularized CAD patients met the inclusion criteria for the main RICCADSA cohort; 267 patients in the observational arm with sleepy OSA phenotype versus patients with no-OSA at baseline were excluded. Of the 244 CAD patients with nonsleepy OSA randomized in the main RICCADSA trial, 1 died and 23 did not come to 1-year follow-up, and thus, 220 patients had analyzable blood samples at both baseline and 1-year follow-up (*n* = 105 in the CPAP group and *n* = 115 in the no-CPAP group) (Figure 1). Baseline characteristics of the nonsleepy patients who did not participate in the current protocol did not differ significantly from the patients who were included in the final analysis except acute myocardial infarction at baseline, which was more common in the studied group (Table 1). The two randomized groups were similar in baseline characteristics, apart from higher aspirin use in the CPAP group (Table 2). In addition, baseline IL-6 levels were significantly higher in the no-CPAP group compared with the values in the CPAP group (*p* = .005) (Table 3).

### CPAP Adherence

All 220 patients were included in the ITT analysis. Of 105 OSA patients allocated to CPAP, 32 (30.5%) returned the device within 12 months; 47 patients (44.8%) achieved the target CPAP usage corresponding ≥4 h/night/every night; median CPAP usage was 3.2 h/night (range 0–9.7). In the no-CPAP group, three patients started CPAP at baseline, and additional three crossed-over within 12 months (Figure 1).

**Table 1**—Baseline Characteristics of the Nonsleepy Patients Participated vs. Not Participated in the Follow-up Study.

	Nonsleepy obstructive sleep apnea			p value
	All ( <i>n</i> = 244)	Included in substudy ( <i>n</i> = 220)	Not included in substudy ( <i>n</i> = 24)	
Age (y)	66.0 ± 8	65.8 ± 8	67.2 ± 10	.440
AHI (/h)	28.7 ± 13	28.6 ± 13	30.1 ± 15	.590
ODI (/h)	16.4 ± 11	16.3 ± 13	17.7 ± 15	.558
ESS score	5.5 ± 2.3	5.5 ± 2.2	4.8 ± 2.3	.126
BMI (kg/m <sup>2</sup> )	28.4 ± 3.6	28.4 ± 3.5	28.2 ± 4.6	.807
Obesity (patients)	68 (27.9%)	61 (27.7%)	7 (29.2%)	.881
Female (patients)	39 (16.0%)	35 (15.9%)	4 (16.7%)	.923
Current smoker (patients)	39 (16.0%)	33 (15.0%)	6 (25.0%)	.204
Pulmonary disease (patients)	16 (6.6%)	16 (7.3%)	0 (0%)	.172
Hypertension (patients)	156 (63.9%)	141 (64.1%)	15 (62.5)	.878
Acute myocardial infarction (patients)	121 (49.6%)	114 (51.8%)	7 (29.2%)	.035
CABG as revascularization (patients)	66 (27.0 %)	58 (26.4%)	8 (33.3%)	.465
Diabetes mellitus (patients)	59 (24.2%)	51 (23.2%)	8 (33.3%)	.270
p-NT-proBNP, ng/L	578 ± 878	542 ± 844	879 ± 1124	.077

Values are mean ± SD (compared using independent student *t*-test) or number of patients (percentage) (compared using chi-squared test or Fisher’s exact test). AHI, apnea–hypopnea index; BMI, body mass index; CABG, coronary artery bypass grafting; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; p-NT-proBNP, N-terminal pro-brain natriuretic peptide.

**Table 2**—Characteristics of the Study Participants.

	Nonsleepy obstructive sleep apnea			p value
	All (n = 220)	No-CPAP (n = 115)	CPAP (n = 105)	
Age (y)	65.8 ± 8	66.2 ± 8	65.4 ± 8	.433
AHI (/h)	28.6 ± 13	29.2 ± 14	27.9 ± 12	.448
ODI (/h)	16.3 ± 13	16.4 ± 12	16.2 ± 10	.901
ESS score	5.5 ± 2.2	5.5 ± 2.2	5.6 ± 2.3	.522
BMI (kg/m <sup>2</sup> )	28.4 ± 3.5	28.5 ± 3.4	28.3 ± 3.7	.626
Obesity (patients)	61 (27.7%)	32 (27.8%)	29 (27.6%)	.973
Female (patients)	35 (15.9%)	17 (14.8%)	18 (17.1%)	.633
Current smoker (patients)	33 (15.0%)	16(13.9%)	17 (16.2%)	.637
Pulmonary disease (patients)	16 (7.3%)	12 (10.4%)	4 (3.8%)	.059
Hypertension (patients)	141 (64.1%)	68 (59.1%)	73(69.5%)	.108
Acute myocardial infarction (patients)	114 (51.8%)	55 (47.8%)	59 (56.2%)	.215
CABG as revascularization (patients)	58 (26.4%)	31 (27.0%)	27 (25.7%)	.835
Diabetes mellitus (patients)	51 (23.2%)	22 (19.1%)	29 (27.6%)	.136
p-NT-proBNP, ng/L	542 ± 844	622 ± 992	464 ± 638	.174
Medication use (patients)				
β-Blocker at baseline	189 (88.3%)	99 (87.6%)	90 (89.1%)	.733
β-Blocker after 1 year	184 (86.0%)	96 (85.0%)	88 (87.1%)	.648
ASA at baseline	192 (89.3%)	96 (85.0%)	96 (94.1%)	.030
ASA after 1 y	193 (90.6%)	98 (86.7%)	95 (95.0%)	.039
Clopidogrel at baseline	118 (54.4%)	58 (50.9%)	60 (58.3%)	.276
Clopidogrel after 1 y	16 (7.5%)	7 (6.3%)	9 (8.8%)	.486
Diuretic at baseline	58 (27.1%)	32 (28.1%)	26 (25.7%)	.672
Diuretic after 1 y	56 (26.2%)	27 (23.9%)	29 (28.7%)	.423
CCB at baseline	38 (17.8%)	18(15.9%)	20% (19.8)	.431
CCB after 1 y	49 (22.9%)	24 (21.2%)	25 (24.8%)	.541
ACE inhibitor at baseline	100 (46.7%)	57 (50.4%)	43 (42.6%)	.249
ACE inhibitor after 1 y	95 (44.4%)	52 (46.0%)	43 (42.6%)	.613
ARB at baseline	36 (16.8%)	20 (17.7%)	16 (15.8%)	.717
ARB after 1 y	41 (19.2%)	23 (20.4%)	18 (17.8%)	.638
Statins at baseline	205 (95.8%)	106 (93.8%)	99 (98.0%)	.125
Statins after 1 y	203 (94.9%)	107 (94.7%)	96 (95.0%)	.905

Values are mean ± SD (compared using dependent *t*-test test) or number of patients (percentage) (compared using chi-squared test). ACE, angiotensin-converting enzyme; AHI, apnea-hypopnea index; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; p-NT-proBNP, N-terminal pro-brain natriuretic peptide.

## Outcomes

### Intention-to-Treat Population

Changes in inflammatory markers over time are shown in [Table 3](#). In both the CPAP and no-CPAP groups, IL-6 decreased significantly from baseline to 1 year. The mean (SEM) change in IL-6 concentration for the CPAP-treated group was 2.8 ± 1.0 pg/mL versus 6.0 ± 1.6 pg/mL in the no-CPAP group (*p* = .102)

([Figure 2A](#)). No significant changes from baseline values were observed regarding hs-CRP, IL-8, and TNF-α ([Table 3](#)).

### Subgroup Analyses

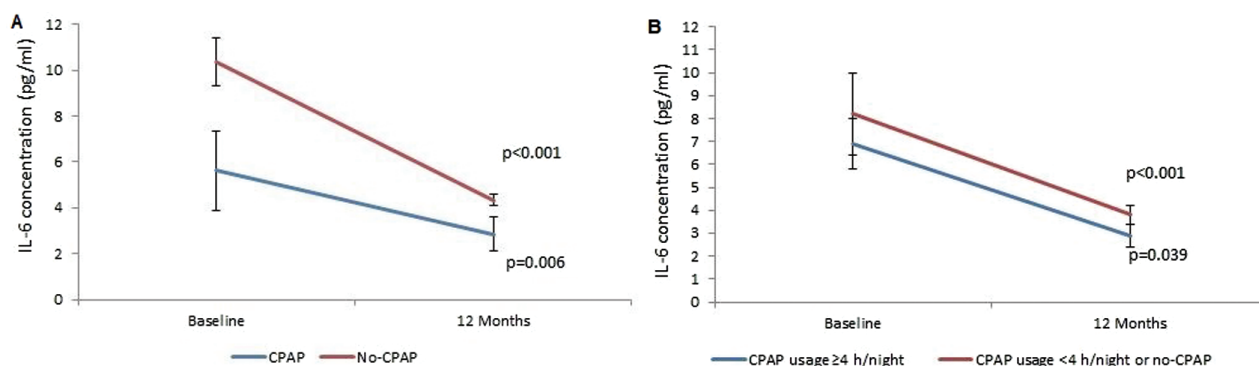
The median value of ESS score was 6 in the study population, and this level was chosen as cutoff value for the categorization of minimally symptomatic versus asymptomatic patients (ESS

**Table 3**—Changes in Inflammatory Markers in Intention-to-Treat Population.

	No-CPAP			CPAP		
	Baseline	12 mo	<i>p</i> value	Baseline	12 mo	<i>p</i> value
IL-6 (pg/mL)	4.2 (2.0, 8.9)*	2.2 (1.8, 4.7)	<.001	3.1 (1.3, 5.6) <sup>†</sup>	2.2 (1.1, 3.9)	.005
hs-CRP (mg/L)	1.6 (0.7, 3.4)	1.3 (0.6, 3.5)	.272	1.9 (0.8, 3.0)	1.7 (0.8, 3.4)	.334
IL-8 (pg/mL)	1.4 (0.9, 2.0)	1.3 (0.9, 2.0)	.378	1.3 (0.8, 1.9)	1.4 (1.1, 2.1)	.252
TNF- $\alpha$ (pg/mL)	5.4 (3.4, 6.9)	4.5 (3.6, 7.0)	.502	5.4 (3.7, 7.4)	4.8 (3.7, 7.1)	.923
ESS score 7–9 ( <i>n</i> = 83)						
IL-6 (pg/mL)	4.0 (1.8, 8.7)	2.6 (1.3, 6.0)	.027	3.7 (1.8, 7.1)	2.5 (1.2, 4.5)	.035
ESS score 0–6 ( <i>n</i> = 137)						
IL-6 (pg/mL)	4.4 (2.2, 9.8) <sup>†</sup>	2.2 (1.2, 4.0)	.053	2.7 (1.2, 5.4) <sup>†</sup>	2.2 (1.1, 3.5)	.005
Non-obese ( <i>n</i> = 159)						
IL-6 (pg/mL)	3.8 (1.9, 7.8) <sup>‡</sup>	2.2 (1.2, 4.5)	.003	3.3 (1.4, 5.5) <sup>‡</sup>	2.5 (1.2, 4.1)	.010
Obese ( <i>n</i> = 61)						
IL-6 (pg/mL)	5.8 (2.4, 12.0)	2.8 (1.1, 4.9) <sup>§</sup>	.020	2.5 (1.1, 5.9)	1.6 (0.7, 3.5) <sup>§</sup>	.143

Values are expressed as median (interquartile range) due to skewed distribution (*p* values calculated using paired *t*-test within the groups). CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IL-8, interleukin-8; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

\**p* = .016, <sup>†</sup>*p* = .020, <sup>‡</sup>*p* = .026, comparing no-CPAP vs. CPAP groups at baseline; <sup>§</sup>*p* = .034, comparing no-CPAP vs. CPAP groups at follow-up.



**Figure 2**—(A) Mean interleukin-6 (IL-6) levels with SE of means at baseline and 1 year in the continuous positive airway pressure (CPAP) and no-CPAP (control) groups; *p* values were calculated using paired *t*-test within the groups. (B) Mean IL-6 levels with SE of means at baseline and 1 year in the CPAP-adherent and non-adherent/no-CPAP (control) groups; *p* values were calculated using paired *t*-test within the groups.

range 1–9; mean value 5.5). There was a significant decrease in IL-6 levels at 1-year follow-up in both ESS subgroups, and the magnitude of change from baseline did not differ significantly even though baseline values were significantly higher in the no-CPAP group among patients with ESS <6 (Table 3). A significant decline in IL-6 values from baseline was observed in both groups among non-obese patients, and only in no-CPAP group among obese patients. Baseline values were higher at baseline in the group allocated to no-CPAP among non-obese patients while higher values were observed at 1-year follow-up in the no-CPAP group among the obese patients (Table 3). The magnitude of changes from baseline tended to be higher in non-obese patients allocated to no-CPAP (*p* = .058).

### On-Treatment Population

In all, 47 out of 105 patients who were allocated to CPAP group and 4 out of 6 patients who crossed-over from the no-CPAP group used the CPAP device 4 h/night or more at 1-year follow-up. The demographic and clinical characteristics at baseline did not differ significantly between the CPAP-adherent and non-adherent/no-CPAP group (Table 4). IL-6 values decreased significantly from baseline to 1 year in both groups (Figure 2B), with no significant between-group difference (the mean  $\pm$  SEM change in IL-6 concentration for the CPAP-adherent group was  $4.0 \pm 1.9$  pg/mL versus  $4.5 \pm 1.1$  pg/mL in the non-adherent/no-CPAP group). No significant changes from baseline values were observed regarding hs-CRP, IL-8, and TNF- $\alpha$  (data not

shown). Applying cutoff levels of CPAP usage 3 h/night or 5 h/night did not change the outcome variables (data not shown).

## DISCUSSION

In this analysis of data from the RICCADSA trial of patients with CAD and nonsleepy OSA, we found no differences in the reduction of circulating inflammatory markers after 1 year of CPAP compared with no CPAP. The only marker that decreased in both study arms was IL-6, with no significant difference between groups. Thus, we could not find evidence to support our hypothesis that CPAP treatment would be associated with reductions in concentrations of circulating inflammatory markers in patients with CAD and concomitant nonsleepy OSA.

The most widely studied circulating markers of inflammation in patients on CPAP treatment are hs-CRP, TNF- $\alpha$ , and IL-6. However, all prospective studies to date have so far enrolled patients exclusively from sleep lab cohorts, and the results have been inconsistent. Based on these studies, treatment with CPAP appears to reduce circulating levels of hs-CRP<sup>13,14,22</sup> and TNF- $\alpha$ ,<sup>23,24</sup> although some studies have failed to detect any changes.<sup>25,26</sup> Even though a meta-analysis showed a trend towards significance for reduction in IL-6 after CPAP treatment,<sup>27</sup> the majority of individual studies have failed to show any effect of CPAP treatment on IL-6 levels.<sup>23,26,28,29</sup> These trials all have included limitations which make it hard to draw any firm conclusions regarding the effect of CPAP treatment on inflammatory biomarkers. In one RCT looking at the effect of CPAP treatment on inflammatory biomarkers, researchers could not find any changes in IL-6 and hs-CRP levels after 2 weeks of

CPAP withdrawal in OSA patients who had been using CPAP.<sup>30</sup> Another recent RCT, conducted in a sleep clinic cohort, did not show any significant effect of 2-month CPAP treatment compared to sham-CPAP on IL-6.<sup>31</sup> All other studies were observational, and some lacked control groups without OSA and/or had a short follow-up period.<sup>14,22,32</sup> In one study, the analysis method used could not detect small changes in CRP.<sup>25</sup> In addition, several studies had small numbers of participants,<sup>22,26,32</sup> with only two including more than 100 patients and having a follow-up of >6 months.<sup>13,29</sup> Of these larger studies, one showed that hs-CRP was reduced after 6 months and 1 year of CPAP treatment in otherwise healthy individuals recently diagnosed with OSA and that these decreases were correlated with CPAP compliance.<sup>13</sup> The other did not report any reduction in IL-6 levels after CPAP treatment.<sup>29</sup>

The results of our RCT in a larger number of patients also failed to document any significant effect of CPAP treatment on inflammatory marker levels in patients with CAD and sleep apnea without daytime sleepiness. It is possible that baseline differences in biomarker concentrations between the CPAP and no-CPAP groups in our study could have contributed to the lack of difference between treatment groups in the reduction from baseline in IL-6 levels. However, even if this did have an influence, the reduction in IL-6 levels associated with use of CPAP was probably too small to be separated from the expected larger reduction seen in all patients after revascularization, where inflammation is reduced due to lifestyle changes (eg, smoking cessation, increased exercise) and new pharmacological therapy (eg, statins, acetylsalicylic acid, etc.). Given the existing data

**Table 4.**—Characteristics of the Study Participants Categorized by CPAP Compliance at 1 y.

	Nonsleepy obstructive sleep apnea			p value
	All (n = 220)	Adjusted CPAP usage <4 h/night or no-CPAP (n = 169)	Adjusted CPAP usage $\geq$ 4 h/night (n = 51)	
Age (y)	65.8 $\pm$ 8	65.9 $\pm$ 8.4	65.8 $\pm$ 7.4	.920
AHI (/h)	28.6 $\pm$ 13	28.5 $\pm$ 13.5	29.1 $\pm$ 12.4	.768
ODI (/h)	16.3 $\pm$ 13	16.3 $\pm$ 11.5	16.4 $\pm$ 10.2	.963
ESS score	5.5 $\pm$ 2.2	5.5 $\pm$ 2.3	5.6 $\pm$ 2.2	.964
BMI (kg/m <sup>2</sup> )	28.4 $\pm$ 3.5	28.6 $\pm$ 3.5	28.1 $\pm$ 3.7	.347
Obesity (patients)	61 (27.7%)	47 (27.8%)	14 (27.5%)	.960
Female (patients)	35 (15.9%)	28 (16.6%)	7 (13.7%)	.627
Current smoker (patients)	33 (15.0%)	27 (16.0%)	6 (11.8%)	.460
Pulmonary disease (patients)	16 (7.3%)	14 (8.3%)	2 (3.9%)	.372
Hypertension (patients)	141 (64.1%)	109 (64.5%)	32 (62.7%)	.819
Acute myocardial infarction (patients)	114 (51.8%)	84 (49.7%)	30 (58.8%)	.253
CABG as revascularization (patients)	58 (26.4%)	46 (27.2%)	12 (23.5%)	.600
Diabetes mellitus (patients)	51 (23.2%)	38 (22.5%)	13 (25.5%)	.656
p-NT-proBNP, ng/L	542 $\pm$ 844	577 $\pm$ 901	444 $\pm$ 618	.235

Values are mean  $\pm$  SD (compared using independent student *t*-test) or number of patients (percentage) (compared using chi-squared test or Fisher's exact test). AHI, apnea-hypopnea index; BMI, body mass index; CABG, coronary artery bypass grafting; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; p-NT-proBNP, N-terminal pro-brain natriuretic peptide.

suggesting that there is a relationship between cytokines and excessive daytime sleepiness,<sup>28</sup> it might also be argued that the main focus on nonsleepy participants in our study might have contributed to the current findings. Further in-depth analysis of the RICCADSA cohort comparing the sleepy and nonsleepy phenotypes may hopefully give more insights in this context.

A number of limitations need to be taken into account when interpreting the results of our analysis. Firstly, because the primary aim of the RICCADSA trial was to investigate the effect of CPAP treatment on cardiovascular mortality and morbidity, the randomization procedure was not designed to take baseline values of inflammatory markers into consideration. This led to a between-group difference in baseline IL-6 values that was not statistically significant but may mask an effect of CPAP treatment in this group. Secondly, we did not include a matched control group without CAD to allow differentiation between changes that could be attributed to an improvement in CAD after revascularization compared with the effects of OSA treatment with CPAP. Thirdly, the natural course of OSA severity as well as inflammatory activity after revascularization is unknown, and this might influence inflammatory marker levels. The fact that we could not find any difference between the CPAP and the no-CPAP group could therefore be due to changes in OSA severity and/or secondary to the stabilization of the CAD per se over the 1-year follow-up period. This is supported by previous studies showing that OSA improves after treatment of underlying cardiovascular diseases.<sup>33</sup> Finally, because all patients were consecutively recruited from a clinical cohort, there is likely to be some heterogeneity with respect to the type of revascularization (CABG or PCI) and in the indication for revascularization (acute, subacute or elective). It is possible that there is a difference in the duration of low-grade inflammation after different types of coronary intervention or based on the underlying indication for revascularization. However, this is also a strength of our study because it means that the results are applicable to everyday clinical practice, rather than only to a highly selected clinical trial population. Another strength of our study is that it is the first RCT to study the effects of CPAP on inflammatory markers in CAD patients with OSA. In addition, it has a large sample size and long follow-up duration.

## CONCLUSIONS

CPAP treatment did not reduce levels of circulating inflammatory markers in revascularized CAD patients with nonsleepy OSA. The decrease in IL-6 levels seen over 1 year of follow-up appears to represent the natural course of this biomarker after myocardial damage and revascularization. It is suggested that concomitant medication and comorbidities other than OSA are more likely to drive this reduction than use of CPAP treatment for nonsleepy OSA.

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