C-Reactive Protein Is Elevated in Heart Failure Patients with Central Sleep Apnea and Cheyne-Stokes Respiration

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Key Words

C-reactive protein · Cheyne-Stokes respiration · Central sleep apnea · Inflammation · Chronic heart failure

Abstract

Background: Manifestation of central sleep apnea (CSA) with Cheyne-Stokes respiration is of major prognostic impact in chronic heart failure (CHF). Inflammatory processes have been linked to a progression of cardiovascular diseases, including heart failure. While an association of C-reactive protein (CRP) levels to obstructive sleep apnea has been documented before, there is a lack of information regarding variation of CRP levels in patients with CSA. **Objectives:** The objective of this study was to investigate a potential association of CRP levels to CSA severity in CHF patients. **Methods:** High sensitivity CRP levels were analyzed in 966 patients with CHF (BMI 26.3 ± 4.6 , New York Heart Association class 2.6 ± 0.5 , left ventricular ejection fraction $29.4 \pm 7.9\%$, N-terminal pro-brain natriuretic peptide, NT-proBNP, level $2,209 \pm 3,315$ pg/ml) without sleep-disordered breathing (SDB; Apnea-Hypopnea Index, AHI, $<5/h$) or various degrees of CSA, documented by in-hospital cardiorespiratory polygraphy or polysomnography. **Results:** The CRP concentration in CHF patients was 0.550 ± 0.794 mg/dl in patients without SDB (AHI 0–4/h, $n = 403$) versus 0.488 ± 0.708 mg/dl

in patients with mild CSA (AHI 5–14/h, $n = 123$, $p = \text{n.s.}$) and 0.660 ± 0.963 mg/dl in patients with moderate CSA (AHI 15–29/h, $n = 160$, $p = \text{n.s.}$). In patients with severe CSA (AHI $\geq 30/h$, $n = 280$), significantly higher CRP concentrations were documented (0.893 ± 1.384 mg/dl, $p < 0.05$). Stepwise regression analysis revealed AHI, NT-proBNP and heart rate to be independently associated with elevated CRP levels. **Conclusion:** Severe CSA in CHF patients is associated with elevated levels of CRP, a systemic marker of inflammation and cardiovascular risk. This might explain in part the negative prognostic impact of CSA in these patients.

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Introduction

In patients with chronic heart failure (CHF) inflammation is associated with an adverse outcome [1–3]. High-sensitivity C-reactive protein (hs-CRP) is a biomarker of inflammation [4, 5]. It has a direct proinflammatory effect on vascular endothelium and is found within atherosclerotic plaques [6, 7]. Subsequently, high CRP level is an established risk factor for coronary artery dis-

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ease [8]. Furthermore, elevated levels of circulating cytokines and CRP levels are closely related to mortality and morbidity in patients with CHF [9].

Obstructive sleep apnea (OSA) is highly prevalent in patients with cardiovascular disease, and is linked to a selective activation of inflammatory processes [10, 11]. Several studies have demonstrated increased levels of inflammatory markers like CRP in patients with OSA [11, 12]. Intermittent hypoxia and sleep deprivation with affecting sympathetic activity may be an explanation [13]. Moreover, there is some evidence for a decrease in CRP levels with appropriate use of nasal continuous positive airway pressure therapy [14].

Recently, central sleep apnea (CSA) with Cheyne-Stokes respiration has been demonstrated as an additional highly prevalent comorbidity in heart failure patients with either reduced or preserved ejection fraction [15, 16]. CSA is caused by impaired hemodynamics (reduced cardiac output, increased pulmonary capillary wedge pressure and/or elevated pulmonary artery pressures) that stimulate pulmonary vagal irritant receptors (J-receptors). In addition, prolonged circulatory times and/or increased sympathetic activity as typical consequences of CHF result in chemoreceptor sensitization, and promote respiratory instability [17–19].

Unlike OSA, CSA has often been regarded as just a marker of heart failure severity. Hence, pathophysiological consequences have not been investigated thoroughly over the past decades. This attitude has changed since CSA was identified as an independent prognostic predictor in patients with CHF [20, 21]. Now there is convincing evidence that marked sympathetic activations are also found in CSA, thus promoting adverse cardiovascular effects resulting in a vicious circle with progression of CSA and further impairment of cardiac function [22].

The aim of the present study was to investigate the interaction between CSA and inflammation. We intended to elucidate a potential association of CSA and CRP levels, exploring whether CSA plays a crucial role in the inflammatory processes of CHF patients.

Material and Methods

Study Design

We conducted a retrospective review of CHF patients screened for sleep-disordered breathing (SDB) between December 2002 and September 2009. Inclusion criteria comprised an impairment of systolic left ventricular function according to echocardiographic criteria (left ventricular ejection fraction, LVEF <45%) and a stable New York Heart Association (NYHA) class $\geq$ II.

Since we intended to investigate CRP levels at different stages of CSA severity, patients with predominant OSA were excluded from this study. Other exclusion criteria included a history of or an ongoing treatment for SDB, significant valvular heart disease, evidence of pulmonary disease, hypercapnia ($p\text{CO}_2 > 45$ mm Hg), pregnancy, acute coronary syndrome or acute myocardial decompensation (defined as intravenous diuretics or catecholamine therapy or intensive care treatment). All patients underwent either full in-hospital polysomnography (PSG) or unattended in-hospital cardiorespiratory polygraphy (PG). Within 2 days of the PSG/PG evaluation, blood samples were collected to determine hs-CRP. In addition, we collected data for demographics, comorbidities (diabetes mellitus, hypertension), blood pressure and heart rate. N-terminal pro-brain natriuretic peptide level (NT-proBNP) was also documented when available. The study was approved by the Ethical Review Board of the Ruhr University Bochum, Bad Oeynhausen.

Methods

hs-CRP Levels. Measurement of hs-CRP concentration was done in the afternoon using the Architect autoanalyzer (Abbott, Wiesbaden, Germany).

Cardiorespiratory PG/PSG and Sleep Data. Sleep studies were performed by either full in-hospital PSG (SOMNOscreen, SOMNOMedics GmbH, Randersacker, Germany) or by in-hospital unattended cardiorespiratory PG (Embletta™, Embla, The Netherlands) as described previously [23, 24]. Sleep disordered breathing was defined in accordance with the 2007 American Academy of Sleep Medicine criteria for scoring respiratory events [25]. If the Apnea-Hypopnea Index (AHI) was <5/h, patients were considered to have no sleep disordered breathing. Patients with an AHI $\geq$ 5/h were classified as having OSA or CSA with Cheyne-Stokes respiration on the basis of the predominant type of SDB. Patients were categorized as no SDB (AHI <5/h), mild CSA (AHI 5–14/h), moderate CSA (AHI 15–29/h) and severe CSA (AHI $\geq$ 30/h).

Echocardiography. Dimensions of the left atrium, left ventricle (end diastolic) and LVEF were measured according to the established guidelines of the American Society of Echocardiography [24, 26].

Cardiopulmonary Exercise Testing. Symptom-limited cardiopulmonary bicycle exercise testing (CPX, ZAN Ferraris) was performed as previously described [24, 27].

Analysis

All analyses were performed using Sigma Plot software (Version 11.0, Systat Software Ltd). Results are reported as mean $\pm$ standard deviation. A p value <0.05 was considered statistically significant. Multiple comparisons among groups of patients with various degrees of CSA/no CSA were performed by using ANOVA. If no normal distribution was found, ANOVA on ranks (Kruskal-Wallis) was performed. Categorical data were compared using χ^2 tests. Spearman's rank correlation was used to detect an association of CRP concentration/AHI and different PSG or clinical data. To assess the relative strength of association between CRP, AHI and possible confounding factors we implemented a multivariate analysis (table 1). We used CRP as the dependent variable and possible confounders/AHI as independent variables. Significant parameters showing differences among groups with various degrees of CSA, as well as sex, arterial fibrillation, ischemic cause and arterial hypertension, were defined as potential confounding variables (table 2).

Table 1. Final model of multivariate analysis: association between CRP and the independent variables of heart rate, NT-proBNP and AHI

	Multiple linear regression		Forward stepwise regression	
	coefficient	p value	coefficient	p value
Heart rate	0.00797	0.038	0.00888	0.015
NT-proBNP	0.0000296	0.030	0.0000296	0.017
AHI	0.00562	0.035	0.00573	0.019

The model was adjusted for age, sex, BMI, diastolic blood pressure, arrhythmia/sinus rhythm, diabetes mellitus, ejection fraction, CPX-VO₂ predicted, creatinine, arterial hypertension and ischemic cause (n = 512; 454 missing observations).

Results

Baseline Data and Sleep-Study Results

Between 2002 and 2009 a total of 1,233 patients with CHF were screened for the presence of SDB by cardiorespiratory PG and 273 patients were screened by PSG. Of these 1,506 patients, 335 (22.2%) with predominant OSA were excluded from analysis as well as 205 (13.6%) with lacking data. Thus, 966 patients with CHF and either concomitant CSA or no CSA were included into this study. CSA was present in 563 patients (58.3%), while 403 (41.7%) presented with no SDB. Other baseline characteristics and sleep study results obtained by PG or PSG are shown in table 2.

hs-CRP Levels

Analysis of CRP concentrations among patients with different levels of CSA revealed a trend towards an increase in CRP concentrations with more pronounced CSA (fig. 1). Compared to mild or no CSA, patients with severe CSA had significantly higher CRP-levels. No differences were observed when evaluating CRP concentrations in patients with moderate CSA compared to patients with mild or no CSA. Comparing patients with moderate to severe CSA (n = 440) with patients demonstrating mild or no CSA (n = 526), we found a significantly higher CRP-level in the moderate to severe CSA group (CRP 0.81 ± 1.25 vs. 0.54 ± 0.78 mg/dl, $p < 0.05$).

When we implemented a multiple linear regression analysis, AHI ($p = 0.035$), NT-proBNP ($p = 0.030$) and heart rate ($p = 0.038$) predicted higher CRP levels. Similarly, using the stepwise linear regression analysis AHI, NT-proBNP and heart rate were independently associated with elevated CRP concentrations.

Evaluating the relationship between inflammation (indicated by CRP) and different sleep parameters using Spearman's rank correlation, we found AHI ($r = 0.138$, $p < 0.001$) and mean desaturation ($r = 0.118$, $p < 0.001$) weakly positive but highly significantly correlated, while mean oxygen saturation ($r = -0.132$, $p < 0.001$) and minimal oxygen saturation ($r = -0.132$, $p < 0.001$) was weakly negatively correlated with CRP-level (table 3; fig. 2). Further analysis of correlations between CRP/AHI and possible confounding variables of clinical and demographic data revealed significant associations, as shown in table 4.

Discussion

In the present study we investigated the relationship between CSA and inflammation in a population of 966 CHF patients. We used hs-CRP as a marker of inflammation and the AHI to assess severity of CSA. Our results demonstrate a significant increase of CRP levels in patients with CHF and severe CSA compared to patients with CHF and no or mild CSA. Furthermore, a weak but significant association between CRP and CSA severity was found.

Previous results raised the question of whether there is an association between SDB and inflammation in CHF. There are several studies that examined an activation of inflammatory pathways in response to OSA syndrome. Shamsuzzaman et al. [12] studied 22 patients with newly diagnosed OSA and found it associated with elevated levels of CRP. Punjabi and Beamer [28] reported a strong association between serum levels of CRP and the degree of SDB in 69 men with or without adjustment for age and several indicators of obesity. Larkin et al. [29] demonstrated that an AHI ≥ 5 /h was associated with increasing levels of CRP in 143 adolescents aged 13–18 years without underlying cardiovascular diseases. Moreover, OSA has been associated with the vascular endothelial alterations that underlie development and progression of atherosclerosis [30]. However, in heart failure patients data on inflammatory activation associated with OSA are scarce.

Similarly, there is little evidence regarding a potential inflammatory response to CSA. A small-scale study conducted by Koyama et al. [31] reported a positive correlation ($r = 0.753$, $p = 0.016$) between the AHI and hs-CRP level in 17 patients with NYHA II or III and an AHI ≥ 15 /h with CSA events in the majority of patients. The results presented here are the first emerging from a large patient cohort. We could demonstrate that patients with severe

Table 2. Demographics, and clinical and sleep variables of the study population

	AHI 0–4/h	AHI 5–14/h	AHI 15–29/h	AHI ≥30/h
n	403	123	160	280
Age ^a , years	60.2±12.4	62.8±14.7*	64.9±11.6*	66.0±10.0*
Male ^a , %	63.7	82.1	82.5	89.3
BMI ^a , kg/m ²	25.6±5.0	26.1±3.8	26.6±4.3	27.3±4.3*,**
Height, cm	171.8±9.1	174.7±9.2*	172.7±8.4	175.2±8.3*,***
Weight, kg	75.8±15.9	79.6±12.8	79.7±15.6	84.0±16.2*
Systolic BP, mm Hg	115.4±19.9	119.5±22.2	113.3±21.3	116.2±26.3
Diastolic BP ^a , mm Hg	70.7±10.5	73.9±12.4	69.8±11.9**	72.5±12.4
Heart rate ^a , min ⁻¹	68.2±12.1	69.2±12.1	71.7±12.7*	73.2±15.7*
Sinus rhythm ^a , %	77.2	77.2	71.3**	61.8
Atrial fibrillation ^a , %	14.1	18.7	20.0	30.0
Pacemaker, %	8.7	4.1	8.7	8.2
NYHA class	2.6±0.5	2.6±0.5	2.6±0.5	2.6±0.5
Ischemic cause ^a , %	37.9	43.1	51.3	56.4
Arterial hypertension ^a , %	49.9	53.6	62.5	67.4
Diabetes ^a , %	23.2	25.0*	37.5	35.6
ACE-/AT1-inhibitors, %	99.0	99.2	96.9	98.6
Beta-blocker, %	95.3	98.4	95.0	94.3
Diuretics, %	94.0	96.7	96.9	95.7
Aldosterone blockers, %	69.0	68.3	72.5	69.2
Digitalis, %	47.6	42.3	45.6	38.0
Amiodarone/sotalol, %	21.1	24.4	29.4	25.4
LVEF ^a , %	30.6±8.1	29.3±8.3	28.2±7.3*	28.6±7.5*
LAD, mm	47.6±7.6	48.8±7.9	51.2±8.3*	52.8±25.4*
LVEDD, mm	67.2±9.6	69.0±9.9	70.3±9.6*	69.9±10.0*
CPX duration, min	7.4±3.3	7.9±3.3	7.3±3.0	6.7±2.5
CPX-WL, W	77.7±34.6	85.9±39.0	75.2±32.7	75.2±31.1
CPX-VO ₂ AT, ml/min/kg	13.1±3.8	13.1±4.2	12.5±3.7	12.0±3.2*
CPX-VO ₂ peak, ml/min/kg	15.5±5.1	15.8±5.3	14.3±4.7	14.2±3.7
CPX-VO ₂ predicted ^a , %	63.6±19.2	62.8±18.9	57.8±18.3*	57.1±16.5*
NT-proBNP ^a , pg/ml	1,734.6±2,738.6	2,211.5±3,702.1	2,374.4±3,057.5*	2,851.3±3,971.8*
Hemoglobin, g/dl	13.6±1.5	14.0±1.5*	13.8±1.8	13.8±1.5
Sodium, mmol/l	138.7±3.6	139.5±3.7	139.0±3.1	139.3±3.5
Creatinine ^a , mg/dl	1.2±0.5	1.3±0.5	1.4±0.5*	1.5±0.5*,**
pH	7.44±0.05	7.44±0.03	7.44±0.03	7.45±0.03*
pO ₂ , mm Hg	77.4±9.7	78.2±10.1	78.7±11.3	75.3±10.4*,**,***
pCO ₂ , mm Hg	37.9±3.7	36.8±3.7	36.5±4.9*	35.3±4.0*,**
Base excess	1.4±2.4	1.1±2.2	1.0±2.4	0.8±2.8*
Results from cardiorespiratory PG/PSG				
Mean SaO ₂ , %	94.4±2.1	93.8±2.2*	93.3±2.1*	92.8±2.1*,**
Min. SaO ₂ , %	87.6±4.6	85.2±4.7*	82.4±5.6*,**	81.6±5.7*,**
Mean desaturation, %	3.0±2.4	4.9±1.4*	5.6±1.5*,**	6.5±2.4*,**,***
Max. apnea duration, s	10.7±15.5	26.4±16.2*	36.0±18.3*,**	38.7±14.4*,**
Max. hypopnea duration, s	24.5±16.7	35.9±10.3*	42.1±12.7*,**	42.5±15.9*,**
AHI/h	2.2±1.3	9.7±2.7	22.4±3.9	42.9±10.8

* p < 0.05 vs. AHI 0–4; ** p < 0.05 vs. AHI 5–14; *** p < 0.05 vs. AHI 15–29. BP = Blood pressure; CPX = cardiopulmonary exercise testing; CPX-WL = maximum workload; LAD = left atrial diameter; LVEDD = left ventricular end-diastolic diameter.

^a These variables were included in multivariate analysis.

Fig. 1. Mean CRP concentrations are significantly elevated in patients with severe CSA (CRP 0.893 ± 1.384 mg/dl) compared to patients with mild CSA (CRP 0.488 ± 0.708 mg/dl) or no SDB (CRP 0.550 ± 0.794 mg/dl).

Table 3. Spearman's correlation between hs-CRP and different parameters of sleep

	r (CRP)	p (CRP)
AHI/h	0.138	<0.001
Mean SaO ₂ , %	-0.132	<0.001
Min. SaO ₂ , %	-0.132	<0.001
Mean desaturation, %	0.118	<0.001
Max. apnea duration, s	0.046	0.154
Max. hypopnea duration, s	0.059	0.069

Table 4. Spearman's correlation between hs-CRP/AHI and possible confounding variables

	r (CRP)	p (CRP)	r (AHI)	p (AHI)
Age, years	0.0567	0.0782	0.207	<0.001
BMI, kg/m ²	0.108	<0.001	0.182	<0.001
LVEF, %	-0.104	<0.05	-0.0957	<0.05
Atrial fibrillation	0.138	<0.001	0.144	<0.001
Ischemic cause	0.0328	0.309	0.152	<0.001

CSA have higher hs-CRP levels compared to patients with mild or no CSA.

Although the pathophysiological mechanisms resulting in CSA are still poorly understood and obviously different from mechanisms responsible for the development

of OSA, both include ventilation arrests with consequent intermittent hypoxias and insufficient sleep, including sleep fragmentation, arousals and sleep deprivation. These mechanisms may link sleep apnea to increased CRP levels, most probably via two main pathways: (1) an increase in concentration of catecholamines caused by sympathetic overactivity [32] and/or (2) increased serum levels in inflammatory cytokines, e.g. caused by reactive oxygen metabolites due to oxidative stress [11, 33]. Both catecholamines and inflammatory cytokines (especially IL-6) trigger CRP biosynthesis and hepatic CRP release [34, 35]. In particular, analyses of Hartmann et al. [36] revealed an upregulation of circulating IL-6, IL-1ra and CRP in response to hypobaric hypoxic conditions at high altitude. Naughton et al. [37] found an elevated sympathetic activity in patients with CHF and CSA compared to patients without CSA indicated by higher urinary and circulating norepinephrine concentrations.

The present study documents a positive correlation among AHI, mean oxygen saturation, minimal oxygen saturation and mean oxygen desaturation on the one hand, and CRP-levels on the other hand (table 3). With respect to this data it is likely that nocturnal hypoxemia contributes to increased CRP levels in patients with more severe CSA. Consistent with our findings, Larkin et al. [29] described CRP to be highly associated with overnight hypoxemia expressed as percentage of sleep time with SpO₂ values <90%. This suggests that hypoxemia may augment release of inflammatory cytokines, adhesion molecules and insulin.

Since a large proportion of OSA patients suffer from coexistent metabolic syndromes/obesity and there is a known, strong correlation between obesity and inflammation [38], complete adjustment is difficult to achieve. In our study population mean BMI was 26.3 ± 4.6 , which is relatively low [12, 28]. However, a significant correlation between BMI and CRP level could also be documented for our patient cohort. Likewise, in accordance with previous studies, we confirmed a significant correlation between levels of CRP as a marker of inflammation and LVEF reflecting severity of CHF, as well as between CRP and atrial fibrillation (table 4) [1, 9, 39, 40].

To assess the relationship between CRP levels and CSA without any confounding effects we implemented a multivariate analysis fitting each parameter that reflected a possible confounder (table 2), including BMI and different clinical and demographic parameters of CHF severity. The results demonstrated an independent association between CRP and AHI as well as between CRP and heart rate, which may reflect the impact of sympathetic activity on inflam-

Fig. 2. Scatterplot showing a significant relationship between AHI and CRP levels ($n = 966$, $r = 0.138$, $p < 0.001$).

matory activity. In addition, results showed an association between CRP and NT-proBNP, while no association was found between CRP and the ischemic cause of CHF. This is striking as inflammation is known to play an important role in the pathogenesis of atherosclerosis [5–8]. Results presented by Koenig et al. [8] confirmed CRP as an independent risk factor for coronary heart disease in a large, randomly selected cohort of initially healthy middle-aged men. Several reasons might be responsible for no such clear association being found for our patient cohort. We did not differentiate between different severity levels of atherosclerosis and coronary artery disease, which could have biased our results. On the other hand, the severity and extent of preexisting heart failure itself is associated with enhanced levels of systemic inflammation [1, 9]. This may have watered down the correlation between ischemia and inflammation in our stable CHF cohort.

CSA in CHF patients represents an independent risk factor for death and cardiac transplantation, and implicates a negative prognostic impact [20, 21]. We hypothesize that this relationship may be in part attributed to enhanced CRP-levels, indicating an inflammatory response to an existing CSA. CRP in particular promotes secretion of inflammatory mediators by vascular endothelium (cytokines, cellular adhesion molecules, endothelin-1, angiotensin-II), reduces secretion of nitric oxide and induces proliferation of smooth muscle cells as well

as apoptosis/necrosis. These alterations may lead to disease progression in patients with heart failure by sustaining endothelial and myocardial dysfunction (cardiomyocyte apoptosis, left ventricular remodeling, contractile dysfunction) and acute negative inotropic effects on cardiomyocytes [10, 41–44].

Correspondingly, raised plasma levels of cytokines seem to be a powerful predictor of an adverse outcome in CHF patients [1–3]. However, several studies have investigated the potential benefit of an antiinflammatory therapy in CHF, e.g. immunoglobulin treatment or statin therapy. These therapies have largely failed to demonstrate benefits in heart failure patients [45, 46]. Adequate treatment of CSA might be an alternative therapeutic option. Targeting an effective suppression of apnea-hypopnea events with consecutive lower nocturnal oxidative stress levels may be associated with antiinflammatory effects in CHF patients. Consistent with this assumption, Koyama et al. [31] measured CHF parameters in 17 patients before and after nocturnal ventilation therapy using adaptive servoventilation. They demonstrated an improvement during therapy for the following parameters: level of brain natriuretic peptide, ejection fraction, NYHA-class, and hs-CRP levels. The change in serum hs-CRP level was negatively correlated with the change in LVEF. They therefore suggested antiinflammatory effects of adaptive servoventilation therapy to be important con-

tributors for improving cardiac function in patients with CHF accompanied by SDB.

Attention should also be paid to other possible mechanisms that may contribute to the negative prognostic impact of CSA in CHF, such as an activation of neurohumoral systems (sympathetic, renin-angiotensin, natriuretic peptides), myocardial ischaemia, surges in blood pressure and heart rate, prothrombotic state and a greater propensity to lethal arrhythmia induced by CSA [21]. Treatment therefore should not only address inflammatory processes, but also focus on improving cardiac function and respiratory stability in CHF patients. Even though preliminary data suggest that with adequate nocturnal ventilation improvements in heart failure status can be achieved, randomized controlled trials are urgently awaited to clarify the impact on mortality, as well as on inflammation in CHF patients.

Limitations

Due to the fact that PSG has only been available at our institution since 2008, most of the patients were investigated by cardiorespiratory PG. We thus could not include parameters regarding sleep duration and fragmentation into this analysis. As the recording time of PSG is generally expected to be lower than the corresponding time of PG, PSG patients present with a higher AHI [47].

In multivariate analysis we found NT-proBNP levels and AHI to be independently associated with hs-CRP levels. However, we cannot derive from this data the proportional impact of each of these variables.

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We did not give preference to screen patients showing hypersomnolence, snoring or breathing disturbances, but attempted to include every patient with CHF who signed in. However, since some of the patients admitted to our sleep lab for PSG came from private practices, this may have caused a small selection bias.

We excluded patients with pure or predominant OSA. Of course this leads to a selected patient cohort, but the major aim of this study was to elucidate the relationship between CSA and inflammation.

Conclusion

This is the first large-scale study demonstrating a significant elevation of CRP level in patients with CHF and severe CSA compared to patients with CHF and mild CSA or no SDB. To what extent the presence of enhanced CRP levels (indicating an inflammatory reaction) contributes to the negative prognostic impact of CSA in CHF patients needs to be further determined. Moreover, the molecular mechanism underlying enhanced CRP-levels in patients with CSA remains unclear. Further studies are warranted to clarify whether adequate therapy of CSA may provide a strategy to improve cardiac outcome by reducing inflammation in these patients.

Financial Disclosure and Conflicts of Interest

The authors declare that they have no conflict of interest.

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