

Homocysteine level in patients with obstructive sleep apnea/hypopnea syndrome and the impact of continuous positive airway pressure treatment

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Conflict of interest

None declared

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Abstract

Background. Obstructive sleep apnea/hypopnea syndrome (OSAHS) is a common disorder in the general population.

Objectives. The aim of this study was to investigate the homocysteine (Hcy) level in the patients with OSAHS of varying degrees and the effect of continuous positive airway pressure (CPAP) treatment on OSAHS patients.

Material and methods. A total of 117 OSAHS patients were recruited and divided into 3 groups (mild OSAHS, moderate OSAHS and severe OSAHS), while 33 non-OSAHS people were selected as control group. For all cases, polysomnography (PSG) variables and the concentrations of Hcy, methane dicarboxylic aldehyde (MDA) and glutathione (GSH) were recorded. Serum Hcy was measured by cyclophorase. The values of MDA and GSH were measured by a spectrophotometer. In the severe OSAHS group, a total of 30 patients received CPAP for more than 4 h every night and were re-examined 6 months later.

Results. The serum levels of Hcy, MDA and GSH showed a significant difference in OSAHS patients and controls. The Hcy and GSH concentrations of OSAHS patients with CPAP treatment showed no apparent change compared with the prior treatment, but the MDA level was obviously lower after CPAP treatment. In controls and the mild/moderate OSAHS groups, multi-element linear regression analysis results indicated that there was a statistically significant relationship between the Hcy concentration and various independent variables (age, MDA, GSH, and the apnea-hypopnea index – AHI).

Conclusions. The change of the Hcy level was not proportional to the severity of the disease in different groups of OSAHS patients, and CPAP did not affect the Hcy levels.

Key words: continuous positive airway pressure, obstructive sleep apnea/hypopnea syndrome, homocysteine

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Introduction

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is a common disorder in the general population, but often underestimated and underdiagnosed.¹ Accumulating evidence reveals that OSAHS is a significant risk factor for acute myocardial infarction and sudden cardiac death in patients with coronary heart disease.^{2,3} The treatment of OSAHS includes continuous positive airway pressure (CPAP), orthodontic devices, weight loss in obese subjects, and positional therapy in episodes of obstructive apnea sleeping supine patients.⁴ McDaid et al. reported that CPAP improved daytime and nighttime blood pressure in patients with moderate and severe OSAHS, highlighting the importance of the management and adherence to CPAP therapy, in particular to normalize the oxygen concentration.⁵ Murri et al., Dorkova et al. and Hernández et al. all reported that treatment with CPAP could attenuate lipid peroxidation in OSAHS patients.^{6–8}

Elevated plasma homocysteine (Hcy) levels have been considered an independent risk factor for cerebrocardiac vascular disease.⁹ Niu et al. reported that the plasma Hcy levels were higher in obstructive sleep apnea (OSA) patients compared to control subjects.¹⁰ Our previous study showed that the concentrations of Hcy were increased in elderly patients with OSAHS, but the levels of Hcy in patients with varying degrees of OSAHS remained disputed.¹¹ Therefore, this study aims to investigate the relationship between the Hcy levels and the severity of OSAHS, before and after 6 months of CPAP treatment.

Material and methods

Participants

Patients who submitted a full polysomnography (PSG) were selected from the Sleep Disorders Center patients in the 1st Affiliated Hospital of Soochow University (Suzhou, China) between June 2008 and December 2015. The participants (patients and controls) suffering from chronic disease, such as chronic obstructive pulmonary disease, liver cirrhosis, thyroid dysfunction, rheumatoid arthritis, chronic renal failure, and/or psychiatric disorders, were excluded from the study. The subjects who took drugs affecting the serum Hcy levels, such as vitamin B₆, vitamin B₁₂ and folic acid, were not included, either. Before examination, information was collected about the general state of the participants, such as age, gender, body height and weight, as well as smoking history and hypertension, based on the final clinical diagnosis (Table 1).

The disease severity was assessed by the apnea-hypopnea index (AHI). For the purpose of analysis, the study population was classified into 4 groups: non-OSAHS (controls, n = 33) with AHI < 5; mild OSAHS (n = 41) with 5 ≤ AHI < 15; moderate OSAHS (n = 40) with 15 ≤ AHI < 30; and severe OSAHS (n = 36) with AHI ≥ 30.

A total of 30 patients with severe OSAHS received CPAP for more than 4 h every night, and the Hcy levels and oxidative stress in patients with OSAHS under CPAP therapy, before and after 6 months of the therapy, were compared. The study was approved by the Ethics Committee of the 1st Affiliated Hospital of Soochow University. All the subjects gave their informed consent.

Polysomnography

A Respironics Alice 4 polysomnographer (Philips Respironics Inc., Murrysville, USA) was used to measure and record overnight PSG parameters, such as electroencephalogram (EEG), electrocardiogram (ECG), electrooculogram (EOG), chin and bilateral anterior tibialis electromyogram (EMG), as well as chest and abdominal movements by strain gauges, nose air current, and pulse oxygen saturation (SaO₂). All the monitoring results analyzed by a computer were assessed by a specially assigned person. Apnea was defined as the cessation in airflow for at least 10 s, and hypopnea was defined as a decrease in the amplitude of the respiratory flow signal of at least 50% for a minimum of 10 s, followed by either a decrease in SaO₂ of 3% or signs of physiological arousal.

Biochemical analysis

Peripheral venous blood samples were obtained at 6 a.m. in the fasting state, after the diagnostic study night. Blood was centrifuged and serum was immediately separated in aliquots and stored at –80°C until assayed. The serum cholesterol, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), serum creatinine (SCr), and fasting plasma glucose (FPG) concentrations were tested by a full-automatic analyzer (AUS400 Olympus, First Chemical Ltd., Tokyo, Japan) on the same day. Creatinine clearance (CCr) was calculated according to the formula for SCr. The serum levels of Hcy were measured by cyclophorase (Jiuqiang Biological Technology Co., Ltd., Shanghai, China). The concentrations of methane dicarboxylic aldehyde (MDA) and glutathione (GSH) were measured by a spectrophotometer (Jiancheng Bioengineering Institute, Nanjing, China).

Statistical analysis

Data was expressed as mean ± standard deviation (SD) for continuous variables. The one-way analysis of variance (ANOVA) was used for the whole difference and the Student-Newman-Keuls test was used for differences between the groups. Correlation was calculated with Pearson's correlation coefficients. We used the χ^2 test to test the distributions of smoking history, hypertension and

gender among the 4 groups of patients. The multiple linear regression analysis was employed to determine variables that affected the Hcy levels. All statistical analyses were carried out using SPSS statistical software, v. 18.0 (IBM Corp., Armonk, USA). Differences were considered significant at $p < 0.05$.

Results

The survey data and basic parameters of all the cases

As shown in Table 1, there were no significant differences among OSAHS patients and controls, concerning gender, age, body mass index (BMI), smoking history, hypertension, and biochemical parameters, such as TC, TG, LDL-C, fasting blood glucose and CCr. The severity of OSAHS was graded according to AHI score, and the higher score indicated the more severe symptoms.¹² The change trend of the oxygen desaturation index (ODI) was consistent with AHI. In addition, the minimal and mean SaO₂ were both decreasing along with the increasing severity of the disease (Table 1).

The homocysteine, methane dicarboxylic aldehyde and glutathione levels

The Hcy, MDA and GSH levels in serum showed a significant difference in the OSAHS patients and controls ($p < 0.05$). Figure 1A shows that the serum concentrations of Hcy were significantly higher in mild and moderate OSAHS patients than in those from the control group,

while they did not differ between severe OSAHS patients and the control group. Similar results were observed in the GSH levels; the serum concentrations of GSH rose noticeably in mild and moderate OSAHS patients, but did not differ between severe OSAHS patients and the control group (Fig. 1B). It is worth noting that the serum concentrations of MDA were higher in severe OSAHS patients than in other groups, and the MDA levels increased with the severity of the disease (Fig. 1C).

The relationship between the homocysteine levels and various independent variables

In the 3 OSASH groups and control group, the Pearson's correlation analysis identified that the serum Hcy level and age were correlated ($r: 0.22, p = 0.009$), and there was also a correlation between Hcy and MDA ($r: 0.32, p < 0.01$) and GSH ($r: 0.74, p < 0.01$), but no correlation between Hcy and AHI ($r: 0.13, p = 0.12$, data not shown). After the severe OSAHS group was removed, the Pearson's correlation analysis identified that the serum Hcy level was positively correlated with AHI ($r: 0.81, p < 0.01$) in the other 3 groups (mild/moderate OSAHS patients and the control group). Furthermore, the multiple linear regression analysis was performed with the changes of Hcy as the dependent variable and the abovementioned related parameters (age, MDA, GSH, and AHI) as the independent variables. There was a significant relation between the Hcy levels and the 4 variables – age, MDA, GSH, and AHI (Table 2) in the 3 groups (mild OSAHS, moderate OSAHS and non-OSAHS).

Table 1. The survey data and basic parameters of all the cases

| Variable | Group | | | |
|------------------------------|----------------------|--------------------------|----------------------------|----------------------------|
| | controls (n = 33) | mild OSAHS (n = 41) | moderate OSAHS (n = 40) | severe OSAHS (n = 36) |
| Age [years] | 44.7 ±10.1 | 42.6 ±8.9 | 40.5 ±12.3 | 41.9 ±8.9 |
| Sex (males/females) | 29/4 | 37/4 | 33/3 | 35/5 |
| BMI [kg/m ²] | 25.08 ±3.35 | 24.36 ±3.61 | 26.49 ±2.78 | 27.34 ±2.82 |
| Smokers [%] | 21.21 | 26.83 | 22.50 | 22.22 |
| Hypertension [%] | 9.09 | 14.63 | 12.50 | 11.11 |
| TC [mM/L] | 4.34 ±1.17 | 4.91 ±0.69 | 4.48 ±1.24 | 4.55 ±1.81 |
| TG [mM/L] | 1.83 ±0.96 | 2.26 ±1.37 | 2.23 ±1.36 | 2.51 ±1.61 |
| FBG [mM/L] | 5.5 ±1.67 | 5.40 ±1.52 | 5.60 ±1.08 | 5.3 ±1.3 |
| CCr [mL/min] | 105.8 ±2.3 | 108.8 ±4.4 | 109.4 ±3.2 | 110.1 ±3.1 |
| LDL-C [mM/L] | 2.46 ±0.45 | 2.50 ±0.62 | 2.28 ±0.38 | 2.48 ±0.53 |
| AHI [events/h] | 3.57 ±0.55 | 10.63 ±2.19 ^a | 22.90 ±3.82 ^{ab} | 42.22 ±8.24 ^{abc} |
| Minimal SaO ₂ [%] | 91.0 ±4.0 | 87.0 ±5.0 ^a | 86.0 ±6.0 ^a | 69.0 ±12.0 ^{abc} |
| ODI [events/h] | 3.6 ±2.2 | 9.7 ±2.5 ^a | 20.3 ±4.8 ^{ab} | 56.7 ±15.4 ^{abc} |
| Mean SaO ₂ [%] | 94.5 ±1.4 | 93.0 ±1.6 ^a | 93.1 ±1.8 ^a | 89.4 ±5.2 ^{abc} |

BMI – body mass index; TC – total cholesterol; TG – triglyceride; FPG – fasting blood glucose; CCr – creatinine clearance; LDL-C – low-density lipoprotein cholesterol; AHI – the apnea-hypopnea index; ODI – oxygen desaturation index; ^a $p < 0.05$ compared to controls; ^b $p < 0.05$ compared to the mild OSAHS group; ^c $p < 0.05$ compared to the moderate OSAHS group; OSAHS – obstructive sleep apnea/hypopnea syndrome, SaO₂ – oxygen saturation.

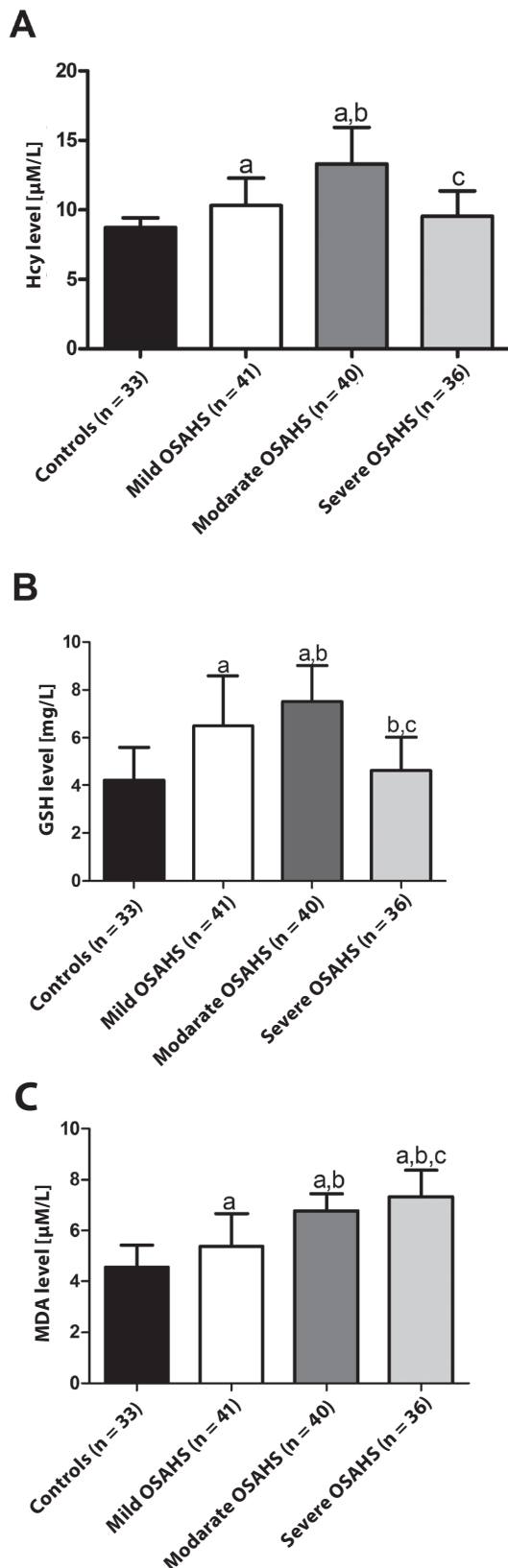


Fig. 1. The Hcy, GSH and MDA levels of all the cases

Hcy – homocysteine; GSH – glutathione; MDA – methane dicarboxylic aldehyde; OSAHS – obstructive sleep apnea/hypopnea syndrome; A – Hcy level; B – GSH level; C – MDA level; data are presented as mean \pm standard deviation (SD); a – $p < 0.05$ compared to controls; b – $p < 0.05$ compared to the mild OSAHS group; c – $p < 0.05$ compared to the moderate OSAHS group.

Table 2. Multiple regression analysis of the relationship between the Hcy levels and various independent variables

| Variables | β | p-value |
|-----------|---------|---------|
| Age | 0.121 | 0.011 |
| AHI | 0.402 | 0.001 |
| MDA | 0.357 | 0.005 |
| GSH | 0.222 | 0.008 |

Hcy – homocysteine; β – standardized regression coefficient; AHI – the apnea-hypopnea index; MDA – methane dicarboxylic aldehyde; GSH – glutathione.

The effects of continuous positive airway pressure treatment on severe obstructive sleep apnea/hypopnea syndrome patients

Continuous positive airway pressure therapy has become a reliable treatment procedure for OSAHS, which improves apnea-hypopnea during sleep as well as the sleep structure. A total of 30 patients with severe OSAHS received CPAP for 4 h every night, and the other 6 patients were not willing to participate in the treatment. During CPAP treatment, 4 patients dropped out due to the intolerance of CPAP. After 6 months of treatment, the Hcy, MDA and GSH levels were detected again in the remaining 26 patients. The Student-Newman-Keuls test results showed that only the MDA levels were significantly lower in severe OSAHS patients with CPAP treatment, while the Hcy and GSH levels were not significantly changed (Fig. 2). Decreased MDA levels were consistent with the reports showing that treatment with CPAP could reduce oxidative stress in OSAHS patients.^{6–8} Thus, MDA may become an effective marker in OSAHS patients who received the CPAP treatment prognosis.

Discussion

This study evaluated the concentration of Hcy, MDA and GSH in patients with OSAHS, and the effect of CPAP on severe OSAHS patients. The Hcy level was higher in the plasma of the patients with OSAHS than in the control subjects, but not proportionally to the severity of OSAHS. Moreover, there was no obvious change in the Hcy plasma level of the patients with CPAP therapy.

Homocysteine is a well-studied marker of cardiovascular disease. Schnyder et al. evaluated the relationship between the Hcy plasma levels on admission and after a successful percutaneous coronary intervention, demonstrating that Hcy was an important independent predictor of future cardiovascular events and cerebrovascular disease.¹³ However, the mechanisms of OSAHS related to cardiovascular disease remain to be investigated despite a vast amount of studies.

The relation between OSAHS and serum Hcy are still under debate. Accumulating evidence has revealed that in all OSAHS patients at different stages of the disease, the Hcy levels were elevated regardless of the presence

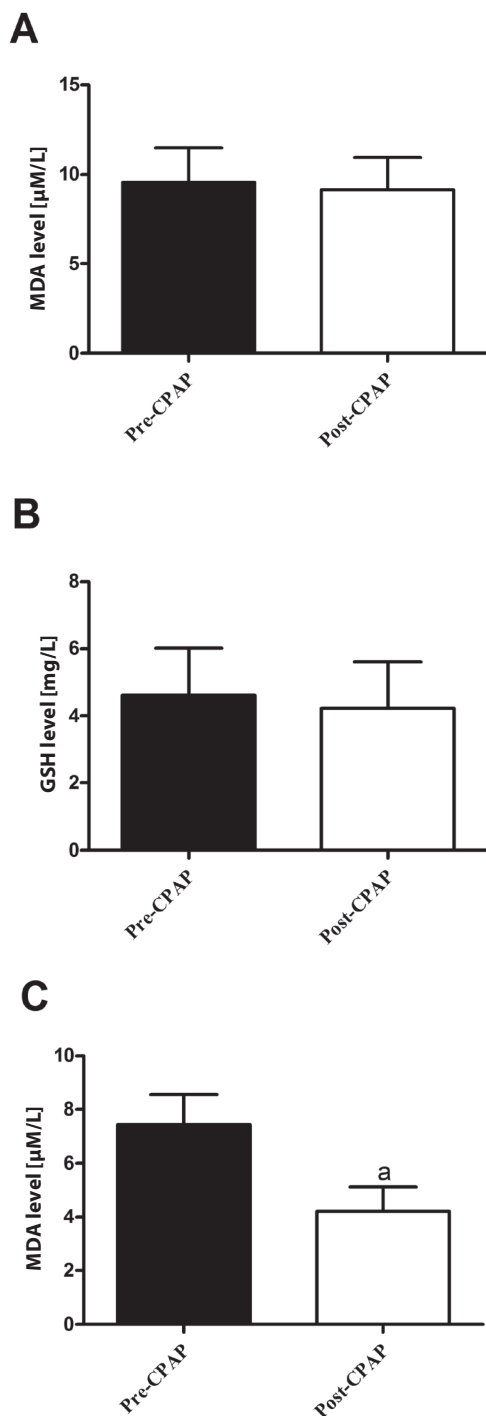


Fig. 2. The effects of CPAP treatment on the Hcy, GSH and MDA levels in severe OSAHS patients

Hcy – homocysteine; GSH – glutathione; MDA – methane dicarboxylic aldehyde; CPAP – continuous positive airway pressure; A – Hcy level; B – GSH level; C – MDA level; data are presented as mean \pm standard deviation (SD); n = 26; a – p < 0.05; post-CPAP vs pre-CPAP.

of cardiovascular disease, and its levels were independently associated with the severity of OSAHS.^{14–16} Meanwhile, Monneret et al. demonstrated that the serum Hcy levels were higher in OSAHS with metabolic syndrome compared to metabolic syndrome patients, and proportional to the severity of OSAHS.¹⁷ However, Cintra et al. observed

that the Hcy plasma levels did not differ between OSAHS patients and the control subjects that were matched for age and sex.¹⁸ The results of those studies were consistent with part of our data showing that the Hcy levels did not differ between severe OSAHS patients and the control group, but were significantly higher in mild and moderate OSAHS patients than in those from the control group. Due to the increased generation of oxygen free radicals in OSAHS patients, GSH, as one of antioxidant defenses, correspondingly increased in order to resist the injury coming from oxidative stress. Furthermore, Hcy serves as an important producer for GSH, and the high levels of GSH will inhibit Hcy degradation in vivo. Hence, the accumulation of Hcy in vivo results in hyperhomocysteinemia (HHcy). Lipid peroxidation is more pronounced in severe OSAHS patients than in mild/moderate OSAHS patients; however, the ability of antioxidants is not enhanced accordingly.¹¹ Thereby, the Hcy level does not further increase in severe OSAHS patients. This mechanism provides further support for the present results and also offers a new clue to explain the conclusion that there was a clear association between slightly elevated blood Hcy levels and early-onset coronary artery disease, peripheral artery disease, cerebrovascular disease, stroke, etc.¹⁹ Also, we noted that the Hcy level was positively correlated with age; this conclusion was similar to previous results.²⁰

Recent studies have shown that oxidative stress exists in OSA patients.^{21,22} As one of the cellular antioxidant defense systems, the amount of GSH is an important indicator of the anti-oxidation ability. Our results showed that the GSH levels rose noticeably in mild/moderate OSAHS patients. Ntalapascha et al. investigated whether systemic oxidative stress was increased in obstructive sleep apnea syndrome (OSAS) patients, and discovered that OSAS might be associated with an increased oxidative burden, possibly via the glutathione/oxidized glutathione (GSH/GSSG) pathway.²³ Being the main product of peroxidation in vivo, MDA is a biomarker of lipid peroxidation injury degree. Our results indicated that the MDA levels increased with the severity of OSAHS. Kilic et al. recently reported that the serum MDA levels are significantly higher in patients with OSAS than in control subjects, and both oxidative imbalance and vascular endothelial dysfunction lead to early development of atherosclerosis, which may cause health-threatening complications of OSAS.²⁴ Therefore, vascular endothelial dysfunction caused by oxidative stress is a predictive factor for the complications of OSAS. In addition, Mancuso et al. compared 3 well-known markers of oxidative stress – advanced oxidation protein products (AOPP), ferric reducing antioxidant power (FRAP) and total GSH – in a cohort of 41 untreated patients with OSAS, indicating that such oxidative stress markers may be useful to detect and monitor redox imbalance in OSAS.²⁵ The present study hinted that there were significant changes in oxidative stress marker levels, and the change of the MDA levels instead of the GSH levels was entirely

consistent with the antioxidant levels in OSAHS patients at different stages of the disease.

For patients with moderate or severe OSAHS, CPAP therapy can obviously alleviate excessive daytime sleepiness and improve the sleep quality, as well as patients' life quality and general well-being.²⁶ Continuous positive airway pressure therapy may decrease the risk of mortality and cardiovascular events in patients with OSA.²⁷ Chen et al. found that the Hcy levels were significantly reduced by CPAP therapy in patients with OSAHS and that the Hcy levels may be clinically recognized as a valuable indicator for the treatment of OSAHS.²⁸ However, we found that the Hcy levels were not noticeably changed in patients undergoing CPAP therapy, which was consistent with the research by Kumor et al., which showed that the Hcy levels did not decline after CPAP therapy for 3 months.²⁹ We also found that the MDA levels were significantly decreased after CPAP therapy, which was similar to a recent study that determined the effectiveness of CPAP therapy in reducing the MDA levels in OSA patients, proving that CPAP therapy yields clinical benefits by reducing oxidative stress in OSA patients.³⁰

In conclusion, the Hcy levels were elevated in mild and moderate OSAHS patients, but not proportionally to the severity of OSAHS. The change of the Hcy level was not proportional to the severity of the disease in different OSAHS groups, and the reason was the increased lipid peroxidation without the accordingly enhanced ability of antioxidants in severe OSAHS patients. Although the CPAP did not affect the Hcy levels, the MDA level was significantly decreased after CPAP in severe OSAHS patients.

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