Lipid peroxidation and paraoxonase activity in nocturnal cyclic and sustained intermittent hypoxia

Article *in* Sleep And Breathing · April 2012

DOI: 10.1007/s11325-012-0703-5 · Source: PubMed

4 authors:

Hacer Kuzu Okur

43 PUBLICATIONS **182** CITATIONS

SEE PROFILE

Zerrin Pelin

Hasan Kalyoncu University

38 PUBLICATIONS **663** CITATIONS

SEE PROFILE

Meral Yüksel

Marmara University

163 PUBLICATIONS **2,801** CITATIONS

SEE PROFILE

Sebnem Yosunkaya

Necmettin Erbakan Üniversitesi

62 PUBLICATIONS **370** CITATIONS

SEE PROFILE

Sleep Breath (2013) 17:365–371
DOI 10.1007/s11325-012-0703-5

ORIGINAL ARTICLE

Lipid peroxidation and paraoxonase activity in nocturnal cyclic and sustained intermittent hypoxia

Hacer Kuzu Okur · Zerrin Pelin · Meral Yuksel · Sebnem Yosunkaya

Received: 28 November 2011 / Revised: 2 March 2012 / Accepted: 3 April 2012 / Published online: 18 April 2012

Abstract
Purpose Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) have been known to be associated with atherosclerosis and hypoxia which was suggested to have an important role in this process by the way of increased oxidative stress. In the present study, we aimed to evaluate the effects of nocturnal hypoxia pattern (intermittent versus sustained) on serum lipid peroxidation and paraoxonase (PON) activity.
Methods Blood collections were performed in 44 OSA, 11 non-apneic, nocturnal desaturated COPD, and 14 simple snorer patients after full-night polysomnographic recordings. Nocturnal sleep and respiratory parameters, oxygen desaturation indexes, serum malondialdehyde (MDA) levels by measuring with the help of the formation of thiobarbituric acid reactive substances (TBARS), and PON activity were assessed in all subjects.
Results OSA and COPD patients showed nocturnal hypoxemia, with a minimum oxygen saturation (SaO_2) in ranges of 53–92 % and 50–87 %, respectively. The mean levels of TBARS was 15.7±3.6 nmol and 15.3±3.4 nmol malondialdehyde (MDA)/ml in OSA and COPD patients, respectively, while the mean level of the control group was 4.1±1.2 nmol MDA/ml. The mean PON activity was found to be 124.2±35.5 U/l in OSA patients and 124.6±28.4 U/l in COPD patients. The mean PON activity of the control group was 269.0±135.8 U/l. The increase in TBARS levels and the decrease in PON1 levels were statistically significant in both OSA and COPD patients according to controls ($p<0.001$ for TBARS as well as PON1).
Conclusion The results of this study revealed that both OSA and non-apneic, nocturnal desaturated COPD patients showed increased levels of lipid peroxidation and decreased PON activity despite the differences in nocturnal hypoxia pattern.

Keywords Intermittent hypoxia · Obstructive sleep apnea · Chronic obstructive pulmonary disease · Paraoxonase · Lipid peroxidation · Oxidative stress

H. K. Okur
Sleep Disorders Unit,
Sureyyapasa Chest Disease Training and Research Hospital,
Istanbul, Turkey

Z. Pelin
Vocational School of Health Related Professions,
Gazikent University,
Gaziantep, Turkey

M. Yuksel
Vocational School of Health Related Professions,
Department of Medical Laboratory, Marmara University,
Istanbul, Turkey

S. Yosunkaya
Meram Medical Faculty, Department of Chest Disease,
Selcuk University,
Konya, Turkey

H. K. Okur (✉)
Mehmet Sengün Sok. Celiker Apt: 6/19, Fenerbahce,
Istanbul, Turkey
e-mail: hacerkuzu@hotmail.com

Introduction

Obstructive sleep apnea syndrome (OSAS) is a disease characterized by repetitive obstruction of the upper airway resulting in an oxygen desaturation, arousal from sleep, and excessive daytime sleepiness. In recent years, OSAS has been associated with cardiovascular diseases such as coronary artery diseases and cerebrovascular events [1, 2].

Intermittent hypoxia–reoxygenation due to repetitive abnormal obstructive events throughout the night is thought to cause the production of free radicals, oxidative stress, and eventually atherosclerosis. Also, patients with chronic obstructive pulmonary disease(COPD) have been reported that there is a significantly higher risk of death from myocardial infarction and they show signs of atherosclerosis which is associated with endothelial dysfunction, hypoxemia, and increased levels of oxidative stress and inflammation biomarkers [3–6].

In OSA, oxygen desaturation occurs in a cyclic manner. Cyclic intermittent hypoxia throughout the night was proposed to be the cause of endothelial dysfunction in OSA patients with early signs of atherosclerosis [7]. Nocturnal desaturation in COPD has been described primarily as REM sleep-associated and occurring in a sustained drop pattern [8]. Nocturnal hypoxemia in COPD is associated with complications, such as arrhythmia and pulmonary hypertension [9], but the association between nocturnal hypoxemia and atherosclerosis has not been investigated previously [10, 11].

High lipid level is one of the major risk factors for cardiovascular diseases. Early development of atherosclerosis may be associated with disorders of lipid metabolism, especially disorders causing lower plasma levels of high density lipoprotein-cholesterol (HDL-C). The HDL-C has been hypothesized to support the efflux of cholesterol from the artery wall or protect the low density lipoprotein (LDL) particle and cell membranes from lipid peroxide-mediated damage [12]. As an HDL-associated enzyme, PON is important for protection of LDL from oxidative modification, which plays a particular role in the development of atherosclerosis [12].

Lavie et al. demonstrated increased levels of lipid peroxidation products and low paraoxonase (PON) 1 levels in OSA patients with cardiovascular diseases and suggested that increased oxidative stress might have a role in cardiovascular morbidity in OSAS. Respiratory disturbance index was a major predictor of an increased oxidative stress in OSA, leading Lavie to propose that intermittent hypoxia was a result of repeated abnormal obstructive events [13]. On the other hand, Yamauchi et al. showed an association between increased oxidative stress markers and oxygen desaturation indexes [14], and Minoguchi et al. implicated the significant correlation between the duration of hypoxia and a lipid peroxidation marker of urinary 8-isoprostane excretion that was suggested to be the result of intermittent hypoxia during the night [15]. Meanwhile, there are several studies about lipid peroxidation and oxidative stress in COPD patients, and increased lipid peroxidation and reduced antioxidant status were documented [16].

Both hypoxia and reoxygenation are important in human pathophysiology. It was postulated that transient hypoxia is followed by cellular reoxygenation injury. Reoxygenation worsens hypoxic injury by increasing reactive oxygen species (ROS) production [17, 18], which is implicated in post-hypoxic cellular injury [19]. Moreover, oxidative stress has been described as an imbalance between ROS production and the capability of biological systems to eliminate reactive intermediates. These reactive intermediates are major components in the pathophysiology of atherogenesis. In OSA patients, cyclic changes in oxygen saturation due to apnea and hypopnea could be thought of as an analogous to ischemia–reoxygenation injury. Initiation of ROS production and repeated cyclic hypoxia–reoxygenation may increase oxidative stress and consequently may have a role in the cardiovascular pathologies frequently reported in OSA patients [20]. Atherosclerosis in COPD patients was postulated that a reduction in flow volumes was a predictive parameter for increased risk of cardiovascular diseases [21, 22]. To the best of our knowledge, the role of nocturnal sustained hypoxia in oxidative stress in daytime normoxic COPD patients has not been reported yet. We thought that nocturnal hypoxemia (seen in either OSA or COPD) might have a role in an increasing oxidative stress that would be evidenced by increased TBARS levels and decreased PON1 activity in both patient groups according to controls.

The purpose of this study was to compare the effect of nocturnal cyclic intermittent hypoxia and sustained intermittent hypoxia on the lipid peroxidation product TBARS and an antioxidant enzyme, PON1. In order to evaluate whether patterns of nocturnal hypoxia affected some parts of the oxidative stress pathway, we compared COPD patients with nocturnal long-term desaturation but normal daytime saturation levels to OSA patients and simple snorers.

Materials and methods

Subjects

This is a retrospective analysis of a group of patients of whom parameters are recorded prospectively. The study was conducted between April 2009 and April 2010, after approval by the Ethics Committee of the Marmara Medical Faculty (MAR.0.01.02/AEK/895). All volunteers provided a written informed consent before participation in the study.

In this study, 44 patients with newly diagnosed OSA, 11 non-apneic COPD patients, and 14 control subjects classified as simple snorers were enrolled.

OSA patients (five women, 39 men) were admitted to the sleep clinic for an initial evaluation, and they had symptoms consistent with sleep apnea as defined by a sleep specialist. Diagnosis of OSA was based on the clinical history, Epworth Sleepiness Scale (ESS) scores [23], and polysomnography (PSG) findings. The diagnosis of OSAS was

confirmed by an apnea–hypopnea index (AHI) of >5 episodes/h of sleep after a full-night PSG.

The non-apneic COPD group (three women, eight men) consisted of 11 stable COPD patients with continuous hypoxemia during sleep as measured by PSG. All patients in this group showed greater than 60 mmHg partial arterial oxygen saturation (PaO_2) during the daytime. Nocturnal oxygen saturation recordings demonstrated more than 30 % of total sleep time with a PaO_2 of less than 90 % in this group. Diagnosis of COPD was based on the European Respiratory Society (ERS) guidelines [24]. A clinical diagnosis of COPD was characterized by chronic cough, exertional dyspnea, or wheezing. Spirometry was performed using a Vitalograph spirometer (Zan, Messgeraete GmbH Germany). Forced vital capacity (FVC) and forced expiratory volume in 1-s (FEV1) measurements were recorded, and the FEV1/FVC ratios were calculated. Airflow limitation was diagnosed when FEV1/FVC was less than 0.7. None of the patients were oxygen dependent and none used bronchodilator treatments. Subjects diagnosed with obstructive or central apnea were not included in the study group.

The control group consisted of 14 patients (three women, 11 men) with symptoms suggestive of OSAS-like snoring, history of apnea, and daytime sleepiness. Polysomnographic findings for this group were compatible with simple snoring with AHI <5.

The exclusion criteria for the study were as follows: (1) connective tissue disorders and metabolic or neurologic disorders inducing peripheral neuropathy (e.g., diabetes mellitus), (2) personal or family history of psychiatric disorders, (3) history of alcohol and drug abuse, (4) infectious diseases, (5) medical illnesses such as cancer and neuromuscular diseases, and (6) use of anti-lipidemic drugs. Patients with histories of cardiac failure were also excluded. The existence of confounding risk factors was determined by routine history analysis and proper medical documentation, physical examination, including blood pressure measurement and laboratory assessments, including total cholesterol, triglyceride, HDL, LDL, and serum fasting glucose levels.

Sleep study

Nocturnal polygraphic recordings included the following variables: electroencephalogram (F3/A2, F4/A1, C3/A2, C4/A1 O1/A2, and O2/A1 according to the 10–20 international electrode placement system), electrooculogram, and chin and anterior tibialis electromyogram and electrocardiogram. Respiration was analyzed with oronasal airflow and thoracic and abdominal strain gauges. Snoring was evaluated with a microphone placed above the larynx. Body position was monitored using a body-position sensor. Oxygen saturation during sleep was measured continuously by finger oximetry. Total sleep time of less than 6 h of the total recording time were not evaluated.

Nocturnal recordings were scored according to the standard criteria of the American Academy of Sleep Medicine [25] in 30-s epoch. An apnea was defined as a cessation of airflow with a duration of ≥10 s. Hypopnea was defined as a ≥50 % reduction in airflow relative to baseline, associated with either arousal or oxygen desaturation of ≥3 %. AHI was calculated as the number of abnormal respiratory events per hour of sleep. As an index of nocturnal oxygen saturation, the minimum oxygen saturation (min O_2), oxygen desaturation index (ODI), and percentage of total sleep time with an oxygen saturation (SaO_2) <90 % were used. Nocturnal continuous hypoxemia was defined as spending more than 30 % of total sleep time with a SaO_2 <90 %.

All blood samples were collected in the morning after an overnight fast, and serum samples were stored at −70°C until they were assayed for paraoxonase 1 (PON1) activity and TBARS levels.

Paraoxonase activity assay

Paraoxonase activity was assessed in serum samples by measuring the initial rate of paraoxon hydrolysis to yield *p*-nitrophenol at 25°C. Serum samples was mixed with an assay buffer contained 1.2 mmol/l paraoxon, 1.32 mmol/l $CaCl_2$, 132 mmol/l Tris-base, and 2.63 mmol/l NaCl (pH 8.5). Absorbances were measured at 405 nm wavelength for 3 min in a spectrophotometer. One unit of paraoxonase activity is defined as 1 μmol of *p*-nitrophenol formed per minute, and activity was expressed as units per liter of serum [26].

Measurement of malondialdehyde level

Serum malondialdehyde levels were measured by the formation of thiobarbituric acid reactive substances (TBARS), based on spectrophotometric measurement. Serum samples were mixed with phosphoric acid, butylated hydroxytoluene, and thiobarbituric acid. The mixture in tubes was incubated in boiling water for 30 min and reaction was stopped with addition the tubes on ice-cold water. MDA was extracted by the addition of *n*-butanol and vortexing for 5 min. The measurements of the pink color of the samples were made with a spectrophotometer at a wavelength of 532 nm. The concentration of TBARS was calculated using 1,1,3,3-tetraethoxypropane as the standard. Results are given as nanomoles of MDA per milliliter of serum [27].

Statistical analysis

Statistical analyses were performed using SPSS 16.00. Data are expressed as mean ± SD. Analysis of variance was used

to find difference between groups and within groups. Non-parametric variables were compared by the chi-square test or Fisher's exact test when the expected value was less than 5. Statistical significance was accepted as $p<0.05$.

Results

The patient population consisted of simple snorers, OSAS, and nocturnal sustained hypoxemic COPD patients. These patients were not age-matched and there were significant age differences between groups (43.8±12.9 years, 49.3±8.5 years, and 57.1±10.4 years, consecutively, $p=0.005$). The groups were matched for gender, body mass index (BMI), and smoking histories. History of hypertension was significantly higher in the COPD and OSA groups than the control subjects ($p=0.002$). There were no statistical differences in the history of ischemic heart disease between the three groups. In the COPD group, there were four smokers, three non-smokers, and four ex-smokers while there were 10 smokers, 13 non-smokers, and 21 ex-smokers in the OSA group. In the control group, there were four smokers, four non-smokers, and six ex-smokers.

Descriptive measurements of clinical properties, nocturnal sleep, and respiratory parameters are presented in Table 1. Serum LDL levels were determined as 127.8±37.1 mg/dl, 111.9±3 2.7 mg/dl, and 117.7±32.2 mg/dl in the OSA, COPD, and control groups, respectively. There were no statistically significant differences between groups. HDL levels were 41.0±7.6 mg/dl, 44.4±13.3 mg/dl, and 42.5±14.0 mg/dl in OSA, COPD, and control groups, respectively. The HDL levels also did not show significant differences between groups.

OSAS and COPD patients showed wide variability in the severity of nocturnal hypoxemia, with minimum SaO_2 ranges 53–92 % and 50–87 %, respectively. Daytime SaO_2 of COPD patients was 92.27 % (range 90–95 %) and daytime arterial carbon dioxide and oxygen pressures were 49.72 and 66.02 mmHg, respectively. The percentage of total sleep time with an SaO_2 <90 % showed a wide distribution range of 33–100 % (mean, 79.7±24.9 %) in COPD patients.

Table 1 presents TBARS and PON1 levels in the OSA, COPD, and the control groups. The mean levels of TBARS were 15.7±3.6 nmol MDA/ml and 15.3±3.4 nmol MDA/ml in OSA and COPD patients, respectively. The mean TBARS level in the control group was 4.1±1.2 nmol MDA/ml. Then mean PON1 levels were 124.2±35.5 U/l in OSA patients and 124.6±28.4 U/l in COPD patients. The mean PON level in the control group was 269.0±135.8 U/l. TBARS levels in COPD and OSA patients were higher than TBARS levels in controls, while PON1 levels in OSA and COPD patients were lower than those in the control group ($p<0.001$ for TBARS as well as PON1).

Discussion

In the present study, it was found that TBARS levels are increased and PON1 activity is decreased in both OSA patients (with cyclic intermittent hypoxia) and COPD patients (with sustained nocturnal intermittent hypoxia), as

Table 1 Characteristics of the OSA, COPD and control subjects

Variables	*Control*	*OSAS*	*COPD*	*P value*
Demographic and clinical data				
Gender				
Male/Female	11/3	40/4	8/3	NS
Age, years	49±8.6	44±13.0	57±10.3	*P=0.005*
BMI, kg/m^2	31.8±4.9	30.5±4.6	28.2±4.5	NS
Respiratory data				
AHI, events/h	2.7±1.0	37.1±23.0	1.7±1.4	*P*<0.001
ODI, events/h		47.2±25.0	14.7±20.2	*P*<0.001
Minimum O_2 %	90.4±0.9	76.6±10.2	70.2±12.8	*P*<0.001
%<90% O2 Sat	0	33.0±18.24	79.7±24.9	NA
Biochemical Data				
Total cholesterol mg/dL	200.2±42.4	205.7±43.6	197.0±29.3	NS
LDL, mg/dL	117.7±32.2	127.8±37.1	111.9±32.7	NS
HDL, mg/dL	42.5±14.0	41.0±7.6	44.4±13.3	NS
Triglyceride, mg/dL	209.2±144.6	200.5±95.9	151.6±42.1	NS
PON1(U/L)	269.0±135.8	124.2±35.5	124.6±28.4	*P*=0.002
TBARS, nmol MDA/mL	4.1±1.2	15.7±3.6	15.3±3.4	*P*=0.000

*Values given as mean (range) unless otherwise noted. *BMI* body mass index; *AHI* apnea-hypopnea index; *ODI* oxygen desaturation index; *NA* not applicable; *LDL* low-density lipoprotein; *HDL* high-density lipoprotein; *PON1* paraoxonase-1; *TBARS* thiobarbituric reactive substances; *NS* not significant.

compared to simple snorers. These results showed that nocturnal intermittent hypoxemia either cyclic or sustained had an effect on increased lipid peroxidation and diminished PON1 activity.

Lipid peroxidation is a major product of an oxidative stress and is often measured by TBARS method and described as MDA equivalents [28]. In our experiment, we show that TBARS levels in OSA and COPD are higher than our control subjects. There are several studies about lipid peroxidation in OSA and COPD patients. Alzoghaibi et al. found that there was an increased lipid peroxidation inhibited by continuous positive airway pressure (CPAP) therapy [29]. Darkova et al. also reported decreased MDA level with the usage of at least four night CPAP machine [30]. Vatansever et al. used a high-performance liquid chromatography method for measurement of lipid peroxidation and found that MDA levels were higher in moderate–severe OSA patients [31]. On the other hand, the level of MDA were reported to be increased in patients with acute exacerbation of COPD compared with healthy smokers in some studies [32], but Stanojkovich et al. notified that there was an increase in MDA levels during discharge not in acute exacerbation of COPD [33]. Our COPD patients were very stable and they do not require any bronchodilator treatment, but they all have nocturnal sustained hypoxia throughout the night. In this perspective, our COPD patients were considered as stable patients.

LDL oxidation is thought to be a major component in the pathogenesis of atherosclerosis [34, 35]. Two mechanisms by which atherogenic-oxidized lipoproteins are removed from the circulation have been suggested. One mechanism is an increased cellular uptake of oxidized lipoproteins and the second is the conversion of oxidized lipoproteins to a less atherogenic lipoprotein [36, 37]. PON probably has a role in both these processes. Under oxidative stress, LDL and HDL are prone to lipid peroxidation. PON is associated with HDL and protects of HDL, rather than LDL, from the harmful effects of oxidative stress [38]. Lavie et al. found significantly lower levels of PON1 activity in OSA patients with cardiovascular disease than in controls. Lavie's results showed that the best correlated parameters were percentage of time below SaO_2 of 9n minimum oxygen saturation, and the respiratory disturbance index (RDI). Of these, Lavie found that the RDI was the best predictor of PON1 level. The authors suggested that abnormal respiratory events cause multiple hypoxia–reoxygenation cycles (cyclic intermittent hypoxia) and lead to decreases in PON1 levels as well as the other parameters of lipid peroxidation. In another study, Vatansever et al. did not find any differences in PON1 activities in OSA patients with respect to their controls, and they concluded that PON activity differ only in OSA patients with cardiovascular disease [31]. Stanajkovic et al. reported similar PON1 activity results in COPD patients that there was only decreased PON1 activity obtained in ischemic heart disease positive COPD patients. The PON1 activity in our OSA and COPD groups were found to be significantly decreased according to controls. The only cardiovascular risk factor in both groups was hypertension, and it might be a confounding factor to decrease PON 1 levels in our study [33].

Increased sympathetic responses to hypoxic chemoreflex stimulation occur in OSA patients. It was reported that similar responses were obtained from healthy subjects exposed to intermittent hypoxia [39, 40]. A research protocol showed that extended exposure to intermittent hypoxia with 20–30 cycles/h for 8–9 h/day for up to 4 weeks [41] resulted in an increased morning blood pressure. These studies suggest that an increase in sympathetic activation emerges in response to cyclic and sustained drops in oxygen saturation. Our findings agree with the previous study in which we showed the similarities of effects of cyclic and sustained nocturnal oxygen drops on the oxidative stress pathway.

Previously, it was reported that oxidative stress is associated with many factors such as hypertension [42, 43], obesity [44, 45], smoking [46, 47], hyperlipidemia [48], and diabetes [49, 50]. In our study population, serum total cholesterol content, HDL and LDL levels, smoking history, and BMI did not differ significantly between OSA, COPD, and control groups. Only the history of hypertension was higher in COPD and OSA groups than in the controls. Matching cardiovascular confounding risk factors to sex, age, and BMI is the desired design for this study. However, our inclusion criteria for the COPD group were very limited. Matching the three groups was thus not possible for us.

One of the major criticisms of our study is that we focused solely on PON1 and TBARS levels as oxidative stress markers. The levels of F_2-isoprostane, superoxide dismutase (SOD), catalase, and erythrocyte glutathione peroxidase are commonly studied parameters in both OSA and COPD patients to show the role of oxidative stress in the development of cardiovascular disease. PON1 activity was also an extensively studied parameter in OSA patients [13, 14], but there were very limited data about PON1 in COPD patients [5, 51]. In the future, it will be helpful to correlate all of the parameters of oxidative stress in both OSA and COPD patients to better study the effects of nocturnal hypoxemia.

In conclusion, our results demonstrate decreased PON1 activity and increased TBARS levels in both OSA and COPD patients in comparison to controls. These results suggest that reduction in the capacities of antioxidative enzymes and increases in toxic lipid peroxidation products might be related to nocturnal hypoxemia. Further studies are needed to explain the effect of nocturnal cyclic and sustained intermittent hypoxia on the oxidative stress pathway.

All authors declare that they have no conflict of interest with this report.

References

1. Peker Y, Kraiczi H, Hedner J, Loth S, Johansson A, Bende M (1999) An independent association between obstructive sleep apnoea and coronary artery disease. Eur Res J 14:179–184
2. Yaggi H, Mohsenin V (2003) Sleep-disordered breathing and stroke. Clin Chest Med 24:223–237
3. Camilli AG, Robbins DR, Lebowitz MD (1991) Death certificate reporting of confirmed airways obstructive disease. Am J Epidemiol 133:795–800
4. MacNee W, Maclay J, McAllister D (2008) Cardiovascular injury and repair in chronic obstructive pulmonary disease. Proc Am Thorac Soc 5:824–833
5. Kluchova Z, Perrasova P, Joppa DZ, Tkacova R (2007) The association between oxidative stress and obstructive lung impairment in patients with COPD. Physiol Res 56:51–56
6. Coulson JM, Rudd JHF, Duckers JM, Rees JLS, Shale DJ, Bolton CE, Cockcroft JR (2010) Excessive aortic inflammation in chronic obstructive pulmonary disease: an ^{18} F-FDG PET pilot study. J Nucl Med 51:1357–1360
7. Lavie P, Lavie L (2008) Cardiovascular morbidity and mortality in obstructive sleep apnea. Curr Pharmaceut Des 14:3466–3473
8. Fletcher EC, Miller J, Divine GW, Fletcher RN, Miller T (1987) Nocturnal oxyhemoglobin desaturation in COPD patients with arterial oxygen tension above 60 mmHg. Chest 92:604–608
9. Fletcher EC, Luckett RA, Goodnight-White S, Miller CC, Qian W, Costarangoz-Galarza C (1992) A double blind trial of nocturnal supplement oxygen for sleep desaturation in patient with chronic obstructive pulmonary disease and a daytime PaO_2 >60 mmHg. Am Rev Respir Dis 145:1070–1076
10. Schünemann HJ, Dorn J, Grant BJ, Winkelstein W Jr, Trevisan M (2000) Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest 118:656–664
11. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM (1996) Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ 313:711–715
12. Mackness MI, Durrington PN, Mackness B (2004) The role of paraoxonase 1 activity in cardiovascular disease. Am J Cardiovasc Drugs 4(4):211–217
13. Lavie L, Vishnevsky A, Lavie P (2004) Evidence for lipid peroxidation in obstructive sleep apnea. Sleep 27:123–128
14. Yamauchi M, Nakano H, Maekawa J, Okamoto Y, Ohnishi Y, Suzuki T, Kimura H (2005) Oxidative stress in obstructive sleep apnea. Chest 127:1674–1679
15. Minoguchi K, Yokoe T, Tanaka A, Ohta S, Hirano T, Yoshino G, Q'Donnell CP, Adachi M (2006) Association between lipid peroxidation and inflammation in obstructive sleep apnoea. Eur Respir J 28:378–385
16. MacNee W (2000) Oxidants/antioxidants and COPD. Chest 117:303–317
17. Chess PR, O'Reilly MA, Sachs F, Finkelstein JN (2005) Reactive oxidant and p42/44MAP kinase signaling is necessary for mechanical strain-induced proliferation in pulmonary epithelial cells. J Appl Physiol 99(3):1226–1232
18. Papaiahgari S, Yerrapureddy A, Hassoun PM, Garcia JG, Birukov KG, Reddy SP (2007) EGFR-activated signaling and actin remodeling regulate cyclic stretch-induced NRF2-ARE activation. Am Respir Cell Mol Biol 36(3):304–312
19. McQuaid KE, Smyth EM, Keenan AK (1996) Evidence for modulation of hydrogen peroxide induced endothelial barrier dysfunction by nitric oxide in vitro. Eur J Pharmacol 307(2):233–241
20. McCord JM (1985) Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med 312:159–63
21. Schünemann HJ, Dorn J, Grant BJ, Winkelstein W Jr, Trevisan M (2000) Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. Chest 118:656–664
22. Friedman GD, Klatsky AL (1976) Siegelaub AB. Lung function and risk of myocardial infarction and sudden cardiac death. N Engl J Med 294:1071–1075
23. Johns MW (1992) Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 15(4):376–381
24. Pauwels RA, Buist AS, Calverley PMA (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Respir Crit Care Med 163:1256–1276
25. Iber K, Ancoli-Israel S, Chesson AL, Quan SF (2007) The AASM manual for the scoring of sleep and associated events. American Academy of Sleep Medicine, Westchester
26. Mackness MI, Harty D, Bhatnagar D, Winocour PH, Arrol S, Ishola M, Durrington PN (1991) Serum paraoxonase activity in familial hypercholesterolaemia and insulin-dependent diabetes mellitus. Atherosclerosis 86:193–199
27. Yagi K (1984) Assay for blood plasma or serum. Methods Enzymol 105:328–31
28. Halliwell B, Chirico S (1993) Lipid peroxidation: its mechanism, measurement, and significance. Am J Clin Nutr 57:715–725
29. Alzoghaibi MA, BaHammam AS (2011) The effect of night of continuous positive airway pressure therapy on oxidative stress and antioxidant defense in hypertensive patients with severe obstructive sleep apnea. Sleep Breath;doi 10.1007/s11325-011-0531-z.
30. Dorkova Z, Petrasova D, Molcanyiova A, Popovnakova M, Tkacova R (2008) Effects of continuous positive airway pressure on cardiovascular risk profile in patients whit severe obstructive sleep apnea and metabolic syndrome. Chest 134:686–692
31. Vatansever E, Surmen-Gur E, Ursavaş A, Karadağ M (2011) Obstructive sleep apnea causes oxidative damage to plasma lipids and proteins and decreases adiponectin levels. Sleep Breath 15:275–282
32. Rahman I, Skwarska E, MacNee W (1997) Attenuation of oxidant/antioxidant imbalance during treatment of exacerbation of chronic obstructive pulmonary disease. Thorax 52:565–568
33. Stanojkovic I, Kotur-Stevuljevic J, Milenkovic B, Spasic S, Vujic T, Stefanovic A, Ilic A, Ivanisevic J (2011) Pulmonary function, oxidative stress and inflammatory markers in severe COPD exacerbation. Respir Med 105:31–37
34. Aviram M (1996) Interaction of oxidized low density lipoprotein with macrophages in atherosclerosis and the antiatherogenicity of antioxidant. Eur J Clin Chem Clin Biochem 34:599–608
35. Steinberg DS, Parthasarathy TE, Carew JC Khoo, Witztum JL (1989) Beyond cholesterol. Modifications of low-density lipoprotein that increase its atherogenicity. N Engl J Med 320:915–924
36. Aviram M (1993) Modified forms of low density lipoprotein and atherosclerosis. Atherosclerosis 98:1–9
37. Mitchinson MJ, Ball RY, Carpenter KL, Enright JH (1990) Macrophages and ceroid in human atherosclerosis. Eur Heart J 11:116–121
38. Aviram M, Rosenblat M, Bisgaier CL, Newton RS, Primo-Parmo SL, La Du BN (1998) Paraoxonase inhibits high-density lipoprotein oxidation and preserves its functions. J Clin Invest 101 (8):1581–1590
39. Leuenberger UA, Hogeman CS, Quraishi S, Linton-Frazier L, Gray KS (2007) Short-term intermittent hypoxia enhances sympathetic responses to continuous hypoxia in humans. J Appl Physiol 103:835–842
40. Gilmartin GS, Lynch M, Tamisier R, Weiss JW (2010) Chronic intermittent hypoxia in humans during 28 nights results in blood

pressure elevation and increased muscle sympathetic nerve activity. Am J Physiol Heart Circ Physiol 299:925–931
41. Tamisier R, Gilmartin GS, Launois SH, Pepin JL, Nespoulet H, Thomas R, Levy P, Weiss JW (2009) A new model of chronic intermittent hypoxia in humans: effect on ventilation, sleep, and blood pressure. J Appl Physiol 107:17–24
42. Rajagopalan S, Kurz S, Münzel T, Tarpey M, Freeman BA, Griendling KK, Harrison DG (1996) Angiotensin II mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation: contribution to alterations of vasomotor tone. J Clin Invest 97:1916–1923
43. Inoue N, Kawashima S, Hirata KI, Rikitake Y, Takeshita S, Yamochi W, Akita H, Yokoyama M (1998) Stretch force on vascular smooth muscle cells enhances oxidation of LDL via superoxide production. Am J Physiol 274:1928–1932
44. Urakawa H, Katsuki A, Sumida Y, Gabazza EC, Murashima S, Morioka K, Maruyama N, Kitagawa N, Tanaka T, Hori Y, Nakatani K, Yano Y, Adachi Y (2003) Oxidative stress is associated with adiposity and insulin resistance in men. J Clin Endocrinol Metab 88:4673–4676
45. Suzuki K, Ito Y, Ochiai J, Kusuhara Y, Hashimoto S, Tokudome S, Kojima M, Wakai K, Toyoshima H, Tamakoshi K, Watanabe Y, Hayakawa N, Maruta M, Watanabe M, Kato K, Ohta Y, Tamakoshi A (2003) JACC Study Group. Relationship between obesity and serum markers of oxidative stress and inflammation in Japanese. Asian Pac J Cancer Prev 4:259–266
46. Harman SM, Liang L, Tsitouras PD, Gucciardo F, Heward CB, Reaven PD, Ping W, Ahmed A, Cutler RG (2003) Urinary excretion of three nucleic acid oxidation adducts and isoprostane F (2) measured by liquid chromatography–mass spectrometry in smokers, ex-smokers, and nonsmokers. Free Radic Biol Med 35:1301–1309
47. Kirkham PA, Spooner G, Ffoulkes-Jones C, Calvez R (2003) Cigarette smoke triggers macrophage adhesion and activation: role of lipid peroxidation products and scavenger receptor. Free Radic Biol Med 35:697–710
48. Ohara Y, Peterson TE, Harrison DG (1993) Hypercholesterolemia increases endothelial superoxide anion production. J Clin Invest 91:2546–2551
49. Cosentino F, Hishikawa K, Katusic ZS, Lüscher TF (1997) High glucose increases nitric oxide synthase expression and superoxide anion generation in human aortic endothelial cells. Circulation 96:25–28
50. Kashiwagi A, Shinozaki K, Nishio Y, Maegawa H, Maeno Y, Kanazawa A, Kojima H, Haneda M, Hikada H, Yasuda H, Kikkawa R (1999) Endothelium-specific activation of NAD(P)H oxidase in aortas of exogenously hyperinsulinemic rats. Am J Physiol 277:976–983
51. Tekes S, Isik B, Yildiz T, Simsek S, Isik MR, Budak T (2010) Chronic obstructive pulmonary disease and paraoxonase 1 192 and 55 gene polymorphisms. Biotechnology & Biotechnological Equipment 24(1):1644–1647