OSAS
oxidative stress and atherosclerosis
Who is the culprit: AHI or ODI

Arie Wollner MD, FCCP
Department of Respiratory Care and Rehabilitation
Sheba Medical Center
OSA as a major public health problem
Arch Intern Med 2002;162:893

- OSAS is a major public health problem due to its ▲ prevalence & profound impact on health & quality of life
- Sleep disordered breathing is detected in ~ 24% of men and ~ 9% of women
- Prevalence of OSAS: > 4% of man & 2% women
Sleep apnea cycle
Clin Chest Med 2010;31:203
OSAS and cardiovascular disease. The role of hypoxemia and inflammation
Eur Respir J 2009;33:1195
Oxidative stress

- Maintaining a stringent cellular oxidation-reduction (redox) balance is essential for homeostasis.
- Oxidative stress: disruption in the balance between oxidant producing systems, and antioxidant defense mechanism.
Reactive oxygen species (ROS)

- ROS represent a class of atoms or molecules capable to chemically react with each other or with other atoms or molecules.
- ROS:
  - $\text{O}_2^\cdot$ superoxide anion
  - $\text{H}_2\text{O}_2$ hydrogen peroxide
  - $\text{OH}^\cdot$ hydroxyl radical
  - $\text{OONO}^-$ peroxynitrite
Reactive oxygen species (ROS)

- The mitochondria are a major source of cellular ROS & oxidative stress
- ~5% of the oxygen consumed during normal aerobic respiration is converted to $\text{O}_2^*$
- In hypoxic re-oxygenation conditions mitochondria becomes dysfunctional to produce even higher amounts of ROS
Reactive oxygen species (ROS)

- ROS are vital regulators of homeostasis as messengers of signal transduction pathways.
- ROS affect a variety of cellular activities & functions by damaging bio-molecules such as lipids, proteins, DNA & carbohydrates.
- Both these consequences of ROS formation; damage to vital macromolecules & altered signaling pathways, are major contributors to the development of cardiovascular morbidities.
Evidence for oxidative stress in OSA
LDL lipid peroxidation in patients with OSAS

Eur Respir J 2000;16:644
Release of superoxide from neutrophils in patients with OSAS

Am J Respir Crit Care Med 2000;162:566

Effect of CPAP on superoxide release

Release of superoxide from neutrophils
In-vitro endothelial apoptosis after hypoxemia re-oxygenation

Vascular endothelial injury in patients with OSAS

Circulation 2008;117:2270
Vascular endothelial injury in patients with OSAS
Effect of CPAP Rx
Circulation 2008;117:2270
OSAS and cardiovascular disease. The role of hypoxemia and inflammation
Eur Respir J 2009;33:1195
Inflammatory pathways in OSA

- Inflammatory cascades are activated in response to chemical and/or physical irritation
- As such, endothelial injury elicits inflammation
Molecular responses to hypoxemia

Circulation 2005;112:2660

Nuclear factor kB (NFkB): master regulator of inflammatory genes expression

Hypoxia Inducible factor-1 (HIF-1): involved with the production of hypoxemia related erythropoietin (EPO), vascular endothelial growth factor (VEGF)
Endothelial-leukocyte interaction during inflammation
Front Biosci 2012;4:1391
Clinical relevance of hypoxemia re-oxygenation in patients with OSAS

Oxygen desaturation index (ODI) = hypoxemia re-oxygenation

$\text{ODI} \leq \text{AHI} \ (\text{AI} + \text{HI})$
Nocturnal oxygen desaturation correlates with the severity of coronary atherosclerosis in coronary artery disease

Chest 2003;124:936

Study objectives: It has been suggested that sleep-disordered breathing (SDB) is a risk factor for ischemic heart disease, and may be associated with increased morbidity and mortality due to cardiovascular disease. The aim of this study was to examine the relation between nocturnal oxygen desaturation (NOD) due to SDB and the Gensini score, which is given to define the severity of coronary atherosclerosis, based on coronary angiograms findings, in patients with coronary artery disease.

Design: We examined the NOD index (ODI) (desaturation of > 3%/events per hour) using pulse oximetry in 59 consecutive patients with coronary artery disease (ejection fraction, > 40%) that was diagnosed by coronary angiography, 30 patients with angina pectoris and 29 patients with old myocardial infarction. The Gensini score was calculated for each patient from the coronary arteriogram. The patients were classified into the following three groups according to the severity of oxygen desaturation: ODI of < 5 events per hour (group N; 16 patients); ODI of ≥ 5 but < 15 events per hour (group A; 27 patients); and ODI of ≥ 15 events per hour (group B; 16 patients). The groups then were examined for the relation between the ODI and the Gensini score.

Results: Of the total number of patients, 72.9% had a nocturnal ODI of more than five events per hour. The Gensini score was significantly higher in groups A and B than in group N, and showed a significant positive correlation with the ODI (R = 0.45; p = 0.01) in all patients. Multiple regression analysis showed that the ODI was the most significant, independent determinant of the Gensini score among the coronary risk factors tested, and that it explained 13.4% of the variance.

Conclusion: These findings suggest that NOD due to SDB may be an important contributor to coronary atherosclerosis in the patients with cardiovascular disease.
Aortic dissection is associated with intermittent hypoxemia re-oxygenation

Heart Vessels 2012;27:265

Table 4 Results of multivariate logistic regression analysis of aortic dissection

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.97–1.06</td>
<td>0.52</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>1.06</td>
<td>0.99–1.14</td>
<td>0.10</td>
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<tr>
<td>Hypertension</td>
<td>1.45</td>
<td>0.50–4.24</td>
<td>0.50</td>
</tr>
<tr>
<td>3% Oxygen desaturation index</td>
<td>1.59</td>
<td>1.21–2.09</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Atherosclerosis in OSAS; Cardiovascular MRI study
Atherosclerosis 2012;222:483
Atherosclerosis in OSAS; Cardiovascular MRI study

Atherosclerosis 2012;222:483
Nocturnal intermittent hypoxemia and development of type 2 diabetes

Diabetologia 2010;53:481
Effect of OSAS with intermittent hypoxemia on platelet aggregation

J Atherosc Thrombosis 2009;16:862
Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link

L. Lavie and P. Lavie

ABSTRACT: Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) is a highly prevalent breathing disorder in sleep that is an independent risk factor for cardiovascular morbidity and mortality. A large body of evidence, including clinical studies and cell culture and animal models utilising intermittent hypoxia, delineates the central role of oxidative stress in OSAHS as well as in conditions and comorbidities that aggregate with it. Intermittent hypoxia, the hallmark of OSAHS, is implicated in promoting the formation of reactive oxygen species (ROS) and inducing oxidative stress. The ramifications of increased ROS formation are pivotal. ROS can damage biomolecules, alter cellular functions and function as signalling molecules in physiological as well as in pathophysiological conditions. Consequently, they promote inflammation, endothelial dysfunction and cardiovascular morbidity. Oxidative stress is also a crucial component in obesity, sympathetic activation and metabolic disorders such as hypertension, dyslipidaemia and type 2 diabetes/insulin resistance, which aggregate with OSAHS. These conditions and comorbidities could result directly from the oxidative stress that is characteristic of OSAHS or could develop independently. Hence, oxidative stress represents the common underlying link in OSAHS and the conditions and comorbidities that aggregate with it.
Sleep disordered breathing and endothelial dysfunction

Neurol Clin 2005;23:1059
OSAS and oxidative stress
Inflammatory pathways in OSA

- Two substances of clinical relevance for the OSA related inflammatory response:

  **Nuclear factor kB (NFkB):** master regulator of inflammatory genes expression

  **Hypoxia Inducible factor-1 (HIF-1):** involved with the production of hypoxemia related erythropoietin (EPO), vascular endothelial growth factor (VEGF)
OSAS, oxidative stress and cardiovascular disease

Eur Respir J 2009;33:1467
Molecular mechanism of cardiovascular disease in OSAS: the oxidative stress link
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Oxidative stress and inflammation in OSA
Front Biosci 2012;4:1391
OSAS and cardiovascular disease. The role of hypoxemia and inflammation

Eur Respir J 2009;33:1195
Respiratory Disturbance Index
An Independent Predictor of Mortality in Coronary Artery Disease

YÜKSEL PEKER, JAN HEDNER, HOLGER KRAICZI, and STEEN LÖTH

Cardiovascular mortality was prospectively investigated in consecutive coronary artery disease (CAD) patients with versus without obstructive sleep apnea (OSA) during a follow-up period of 5 yr. An overnight sleep/ventilatory study was performed in patients requiring intensive care (n = 62, mean age 67.6 ± 10.4 yr, range 44 to 86) during a stable condition (New York Heart Association [NYHA] functional class I-II) 4 to 21 mo after discharge from the hospital. OSA, defined as a respiratory disturbance index (RDI) of 10/h or more was found in 19 patients (mean RDI 17.5 ± 8.3). Three OSA subjects who were successfully treated with continuous positive airway pressure (CPAP) during the observation period were excluded from the final analysis. There was no statistically significant difference (Fisher two-tailed exact test) between the OSA and non-OSA patient groups in terms of number of elderly subjects (age ≥ 65 yr), gender, obesity (body mass index [BMI] ≥ 30 kg/m²), smoking history, presence of hypertension, diabetes mellitus, hypercholesterolemia, or history of myocardial infarction at the study start. During the follow-up period, cardiovascular death occurred in six of 16 OSA patients (37.5%) compared with 4 (9.3%) in the non-OSA group (p = 0.018). The univariate predictors of cardiovascular mortality were RDI (p = 0.007), OSA (p = 0.014), age at baseline (p = 0.028), hypertension at baseline (p = 0.036), history of never-smoking (p = 0.031), and digoxin treatment during the follow-up period (p = 0.013). In a Cox multiple conditional regression model, RDI remained as an independent predictor of cardiovascular mortality (exp β = 1.13, 95% confidence interval [CI] 1.05 to 1.21, two-sided p < 0.001). We conclude that untreated OSA is associated with an increased risk of cardiovascular mortality in patients with CAD. Furthermore, it appears appropriate that RDI is taken into consideration when evaluating secondary prevention models in CAD.
Molecular response to normoxemia, sustained hypoxemia, intermittent hypoxemia-reoxygenation
Circulation 2005;112:2660