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CLINICAL REVIEW

# Oxidative stress in obstructive sleep apnea and intermittent hypoxia – Revisited – The bad ugly and good: Implications to the heart and brain

Lena Lavie*

*The Lloyd Rigler Sleep Apnea Research Laboratory, Unit of Anatomy and Cell Biology, The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, POB 9649, 31096 Haifa, Israel*

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SUMMARY

Obstructive sleep apnea (OSA), characterized by intermittent hypoxia (IH), is linked with increased reactive oxygen species/reactive nitrogen species (ROS/RNS) and oxidative stress, which adversely affect the associated cardio-/cerebro-vascular disease in OSA. Yet, animal and a small number of human studies support activation of cardio-/cerebro-protective mechanisms as well. ROS/RNS are intricate and multifaceted molecules with multiple functions. At low-moderate concentrations ROS/RNS are considered "good", by regulating vital cellular functions. At higher levels, they are considered "bad" by promoting oxidative stress and damaging vital macromolecules through ischemia and reperfusion (I/R) injury. Subsequently, ROS/RNS can get "ugly" by eliciting sterile inflammation and a multitude of deadly pathologies. What makes ROS/RNS good, bad, or ugly? A dynamic interplay between a large number of factors determines the outcomes. These include the types of ROS/RNS produced, their quantity, duration, frequency, intracellular localization, micro-environmental antioxidants, as well as the genetic make-up and life style related variables. This review presents the currently available data on redox biology in physiological/pathophysiological conditions and in OSA/IH, in order to better understand the apparently contradictory findings on damage vs. repair. These findings are discussed within the context of the prevailing views on I/R associated ROS/RNS, and their potential implications to OSA.



## Introduction

Obstructive sleep apnea (OSA) is a highly prevalent breathing disorder in sleep. It is characterized by intermittent hypoxia (IH) leading to blood hypoxemia, hypercapnia, sleep fragmentation, augmented respiratory efforts and increased sympathetic activity [1]. At least 4% and 2% of adult men and women of the general population are diagnosed with OSA and its characteristic symptoms [1]. The prevalence of sleep disordered breathing (SDB) in men and women not displaying day time somnolence may rise up to 24% and 10%, respectively. In obese and elderly populations these values rise to 60% [2]. OSA is also an independent risk factor for cardiovascular morbidity [3–5], and its prevalence is higher than 60% in patients after acute myocardial infarction (AMI) or stroke [6,7]. Moreover, the incidence of cardiovascular morbidities such as hypertension, ischemic heart disease, chronic heart failure, arrhythmias and strokes was also shown to be higher than in the general population [3], thus, making OSA a major public health problem by affecting patient's health and quality of life [8]. These latter findings prompted a great number of studies over the past decade aimed at elucidating the impact of OSA on the cardio- and cerebro-vascular system and the associated comorbidities. However, the underlying mechanisms of this association are complex and intertwined and not entirely understood.

Oxidative stress and concomitant inflammation are two of the prominent underlying mechanisms suggested to explain this association. The former is defined as an imbalance between pro-oxidant and anti-oxidant systems resulting in excessive production of reactive oxygen species (ROS). The latter is the body's response to a variety of external as well as internal insults including

* Tel.: +972 4 8295234; fax: +972 4 8343934.
*E-mail address:* lenal@tx.technion.ac.il.

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**Abbreviations**

| | |
|---|---|
| AHI | apnea–hypopnea index |
| AMI | acute myocardial infarction |
| AP1 | activator protein1 |
| $BH_4$ | tetrahydrobiopterin |
| CAD | coronary artery disease |
| CD | cluster of differentiation |
| cGMP | cyclic GMP |
| CNS | central nervous system |
| COPD | chronic obstructive pulmonary disease |
| eNOS | endothelial NOS (NOS3) |
| EPCs | endothelial progenitor cells |
| EPO | erythropoietin |
| Erk1/2 | extracellular signal-regulated kinase |
| GPx | glutathione peroxidase |
| GSH | glutathione (reduced) |
| GSSG | glutathione disulfide (oxidized) |
| $H_2O_2$ | hydrogen peroxide |
| HDL | high-density lipoprotein |
| HIF-1α | hypoxia inducible factor-1α |
| HNA | 4-hydroxy-2-nonenal |
| HO-1 | heme oxygenase 1 |
| HSPs | heat shock proteins |
| ICAM-1 | intracellular cell adhesion molecule 1 |
| I/R | ischemia and reperfusion |
| IH | intermittent hypoxia |
| IL-8 | interleukin 8 |
| IL-6 | interleukin 6 |
| iNOS | inducible NOS (NOS2) |
| IPC | ischemic preconditioning |
| Keap1 | Kelch-like ECH-associated protein 1 |
| LAD | left anterior descending artery |
| LDL | low-density lipoprotein |
| MDA | malonaldehyde |
| MI | myocardial infarction |
| mPTP | mitochondrial permeability transition pore |
| NAC | N-acetylcysteine |
| NADPH | reduced nicotinamide adenine dinucleotide phosphate |
| nCPAP | nasal continuous positive airway pressure |
| NFκB | nuclear factor κB |
| nNOS | neuronal NOS (NOS1) |
| NO | nitric oxide |
| NOS | nitric oxide synthase |
| Nox | NADPH oxidase |
| Nrf2 | nuclear factor (erythroid-derived 2)-like2 |
| $O_2^{\bullet-}$ | superoxide anion |
| ODI | oxygen desaturation index |
| $OH^{\bullet}$ | hydroxyl radical |
| $OONO^-$ | peroxynitrite |
| OSA | obstructive sleep apnea |
| oxLDL | oxidized LDL |
| p38 MAPK | p38 MAP kinase |
| PAC-1 | specific marker for glycoprotein (GP)IIb/IIIa |
| PI3K | phosphatidylinositol-3-kinase |
| PKC | protein kinase C |
| PON-1 | paraxonase-1 |
| PSLG-1 | P-selectin glycoprotein ligand 1 |
| Redox | oxidation/reduction balance |
| RNS | reactive nitrogen species |
| ROS | reactive oxygen species |
| SDB | sleep disordered breathing |
| SH | thiol |
| SOD | superoxide dismutase |
| TBARs | thiobarbituric acid reactive substances |
| TNF-α | tumor necrosis factor α |
| VCAM-1 | vascular cell adhesion molecule 1 |
| VEGF | vascular endothelial growth factor |
| VEGF-R2 (KDR) | VEGF receptor 2 |

oxidative stress. This association between oxidative stress and inflammation makes both mechanisms tightly interconnected and exacerbating each other [9,10].

The involvement of oxidative stress and inflammation and their potential role in promoting cardiovascular morbidity in OSA were extensively described in a review published in this journal in 2003 [11]. In that paper it was suggested that intermittent hypoxia (IH) – the hallmark of OSA – characterized by profound hypoxic episodes followed intermittently by rapid blood oxygenations could be considered analogous to repeated ischemia and reperfusion (I/R) events which result in injury due to flux of ROS during the reperfusion period. I/R injury is a well-established oxidative stress pathway for generating endogenous ROS. It occurs when blood flow to tissues or organs is disrupted and subsequently restored [12]. In a similar manner, the nightly IH cycles OSA patients experience promote ROS production and oxidative stress through these pathways, as shown over the last decade [11,13].

ROS molecules damage a multitude of vital biomolecules, hence, affecting a vast number of pathologies. Therefore, they are considered "bad/ugly" [14]. Despite their injurious nature, by acting like a double-edged sword, ROS are also considered "good". While at **high quantities** ROS promote inflammation and injury, at **low or moderate concentrations**, ROS act in vital signaling pathways essential for repair and survival. This dual activity is exemplified in various morbidities. In cancer cells, for instance, ROS activate intracellular signaling cascades that maintain the oncogenic phenotype but also possess anti-tumorigenic activity by inducing cell death [15]. Ischemia and reperfusion (I/R) is another well-established phenomenon demonstrating the dual functions of ROS. Although I/R is mostly known as a pathway for eliciting ROS production and subsequent injury, paradoxically, in many instances several brief and intermittent cycles of I/R were shown to exert **protective** rather than damaging effects. These protective effects, termed **ischemic preconditioning (IPC)**, were demonstrated in various organs including the heart and brain.

Favorable/unfavorable effects of ROS in physiology and pathophysiology are two sides of the same coin [13]. Over the last decade, a great number of studies and reviews were dedicated to the unfavorable effects of IH-associated ROS, as oxidative stress, inflammation and the resultant cardio–cerebro-vascular morbidities in OSA. However, evidence supporting potential protective effects in OSA/SDB/IH is also emerging. It is mainly provided by controlled animal studies mimicking OSA and from recent cellular and epidemiological studies.

This review is aimed at integrating the currently acquired knowledge on redox biology with the currently emerging knowledge on redox biology in OSA/IH while focusing on the complexity of I/R associated damage and repair. This may allow to implement the massively acquired data demonstrating the intertwined unfavorable/favorable effects of redox biology and further stimulate the interest and understanding in this expanding field of research. As such, this may also facilitate the search for detecting potential markers for protective mechanisms associated with IH and OSA/SDB to identify who runs a greater or lower risk for associated morbidities.