Nitric oxide (NO) is an almost ubiquitous signaling molecule in the human body that is involved in numerous biological functions, including regulation of vascular tone, inflammation and neurotransmission. It plays a major role in the regulation of blood pressure, the prevention of blood clotting, the dilation of blood vessels and the destruction of pathogens. Nitric oxide is used extensively in medical treatment; for example, nitroglycerin ameliorates the pain of angina by providing nitric oxide to the blood vessels that supply the heart. Another example is the popular drug Viagra, which controls penile erection by regulating nitric oxide.

In 1991 nitric oxide was first discovered in the exhaled breath of humans and other vertebrates. Later it was discovered that nitric oxide concentration in exhaled breath was strongly dependent on the exhalation flow rate. This, interestingly, was significantly different from other endogenous gases (e.g., carbon dioxide and nitrogen). A major advantage of the flow-independent nitric oxide parameters is that researchers can partition fractional exhaled nitric oxide (FENO) into two important anatomic subdivisions of the lungs: the airway and alveolar regions, each having their own pathologic involvement. This, in turn, leads to the use of nitric oxide as a biomarker for, among other pathologies, inflammatory lung diseases and sleep apnea.

However, accurate measurement and interpretation of exhaled nitric oxide must be considered carefully. Nitric oxide is a free radical that serves as a messenger for cellular signaling and physiological reactions such as inflammatory responses in vivo. Appropriate levels of nitric oxide production are important in protecting various organs including the liver and heart from ischemic damage.

**NITRIC OXIDE & OBSTRUCTIVE SLEEP APNEA**

Recurrent episodes of obstruction in the upper airway during sleep result in pathophysiological changes that may predispose humans to vascular diseases. Researchers have found that nitric oxide may be one of the mediators for these changes.

Obstructive sleep apnea (OSA) is one of the most common types of sleep disorders and is characterized by repetitive episodes of complete or partial upper airway obstruction during sleep. OSA is accompanied by hypoxemia, hypercapnia, reoxygenation, changes in intra-thoracic pressure and arousals. This leads to an increased risk of cardiovascular disorders including hypertension, congestive heart failure (systolic and diastolic dysfunction), cardiac arrhythmia (e.g., bradycardia, A-V Block and atrial fibrillation), and cardiac ischemia (coronary artery disease, myocardial infarction, nocturnal ST-segment depression and nocturnal angina). The main intermediary mechanisms in the pathophysiology of OSA are: changes in the sympathetic activation leading to vasoconstriction, increased catecholamines, tachycardia and impaired cardiovascular variability; increased coagulation; metabolic dysregulation that contributes to problems such as insulin resistance and obesity; endothelial dysfunction; and inflammation.

A study conducted in Hong Kong found that circulating nitric oxide is suppressed in OSA, and this suppression is promptly reversible with the use of nasal continuous positive airway pressure (CPAP) therapy. The findings support the idea that nitric oxide is one of the mediators involved in the acute hemodynamic regulation and long-term vascular remodeling in OSA.2

In a recent French study, changes in sleep-wake states and nitric oxide were examined in rats at baseline and again in response to a 24-hour paradoxical sleep deprivation. The authors reported that cortical nitric oxide release exhibits a circadian rhythm with higher amplitude in aged rats than in young-adult rats. However, after paradoxical sleep deprivation, a limited overproduction of nitric oxide is obtained in older rats compared with young-adult rats.3 Due to these characteristics of nitric oxide, patients with OSA have an impairment of resistance-vessel endothelium-dependent vasodilation.

Nitric oxide has been associated not only with exhaled concentration but also with plasma concentration. For example, investigators in another study compared overnight plasma concentrations of nitric oxide in sleep apnea patients before and after CPAP treatment. They found a significant increase in nitric oxide concentrations and levels of the amino acid L-arginine after treatment. This suggests that sleep apnea is associated with a chronic state of diminished circulating nitric oxide concentrations that can be ameliorated by CPAP treatment.4 In addition to CPAP therapy, it also has been shown that oxygen administration improves the serum level of nitric oxide metabolites in patients with OSA.5

**NITRIC OXIDE & UPPER AIRWAY INFLAMMATION**

The main features of pulmonary pathologies (e.g., interstitial lung disease and pulmonary hypertension) appear to be immune activation and vascular endothelial cell injury. Interstitial and alveolar inflammation also appear to be associated with these pathologies.6

It is important to note that cytokine-mediated upregulation of the inducible isof orm of nitric oxide synthase (iNOS), leading to the production of large quantities of nitric oxide, accompanies the immune-inflammatory processes. Excess nitric oxide generation appears to apply strong proinflammatory and cytotoxic properties and relate to the pathogenesis of autoimmune diseases. The origin and increase/decrease of upper airway inflammations are poorly understood, partially because some studies are limited by the lack of standardization in expiratory flow rates and exclusion of the nasopharynx, both having dramatic effect on exhaled nitric oxide concentrations. Recommendations for stan-
Inflammation is present in patients with sleep apnea.10-12 Moreover, surrogate biomarkers, including nitric oxide release during ageing in the rat. Neuroscience. 2003;116(3):863-70.


