OSA and Cardiovascular Disease
The Oxidative Stress Connection

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Objectives

Describe the role of OSA and heart disease

Describe the role of oxidative stress in inflammation and heart disease

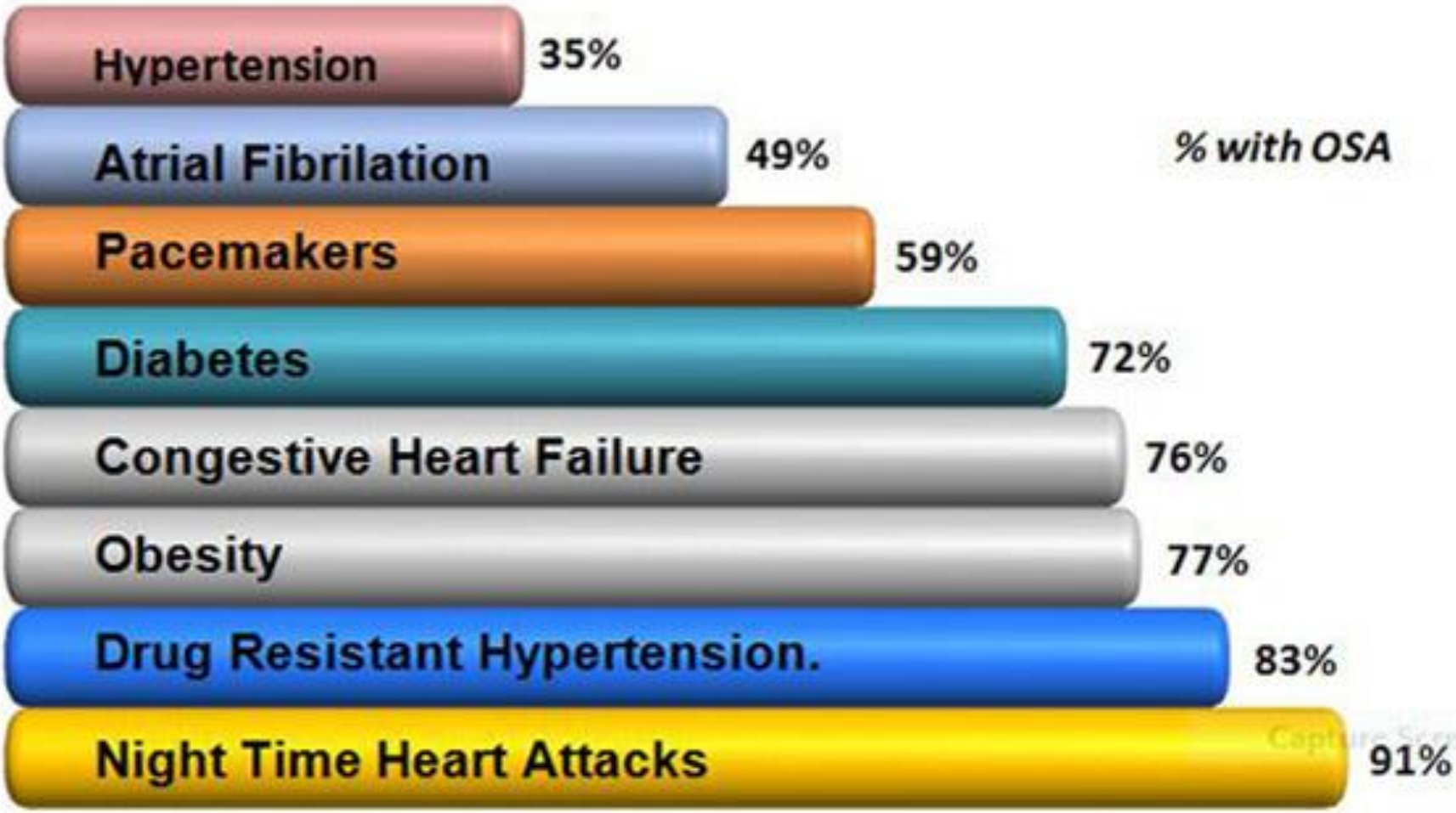
Describe the role of oxidative stress in metabolic syndrome and diabetes

Describe the role of NCPAP in reducing oxidative stress

Describe the role of NCPAP in improving heart disease

Background of OSA and Oxidative Stress (Free Radicals)

Diseases Associated with OSA



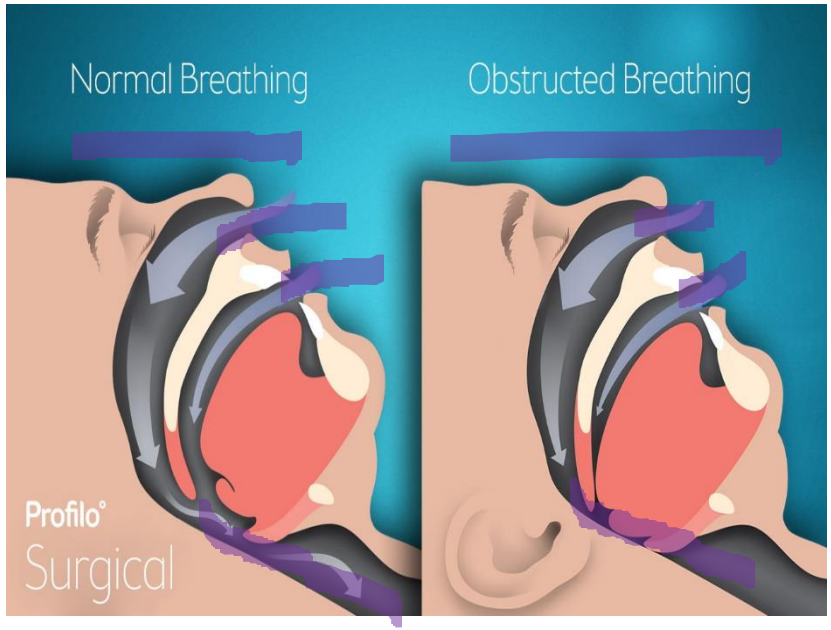
OSA- Obstructive Sleep Apnea

OSA

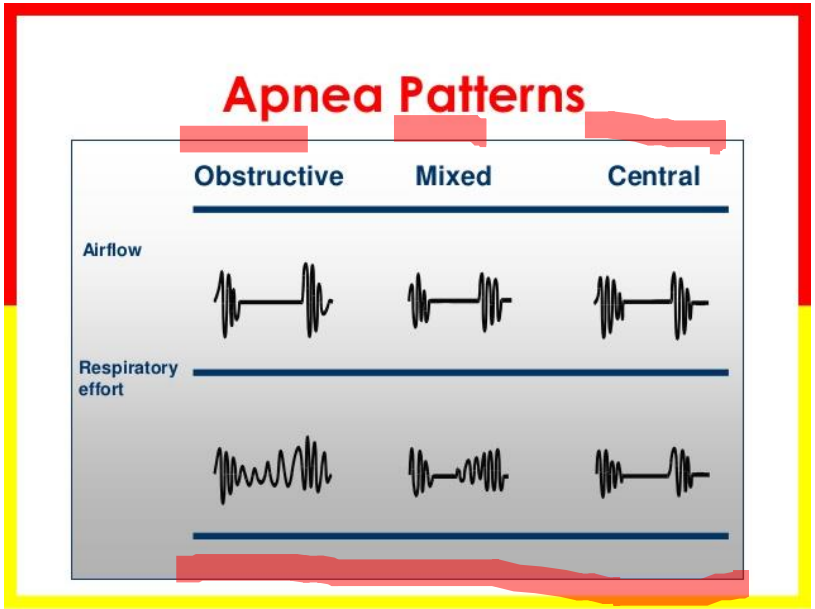
- Highly prevalent breathing disorder
- Risk factor for cardiovascular mortality

OSA

- Intermittent and recurrent pauses in breathing with intermittent hypoxia



Apnea Hypopnea Index (AHI)	
Severity	AHI per Hour
None/Minimal	< 5
Mild	5 -15
Moderate	16-30
Severe	> 30

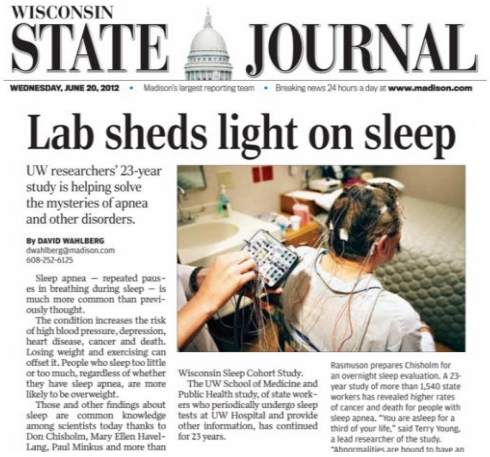


Apnea and AHI

Obstructive Sleep Apnea and Hypertension

Wisconsin Sleep Cohort Study

- The Wisconsin Sleep Cohort (WSC) is an ongoing longitudinal study of the cause's consequences and natural history of sleep disorders, particularly sleep apnea, now in its 23rd year.
- Dose-dependent relationship between severity of sleep apnea and risk of developing hypertension
- Odds for developing hypertension during a 4–8-year follow-up period
  - 2.0 if AHI was 5-15
  - 3.0 if AHI>15



WISCONSIN STATE JOURNAL

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Lab sheds light on sleep

UW researchers' 23-year study is helping solve the mysteries of apnea and other disorders.

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Sleep apnea – repeated pauses in breathing during sleep – is much more common than previously thought.

The condition increases the risk of high blood pressure, depression, heart disease, cancer and death. Losing weight and exercising can offset it. People who sleep too little or too much, regardless of whether they have sleep apnea, are more likely to be overweight.

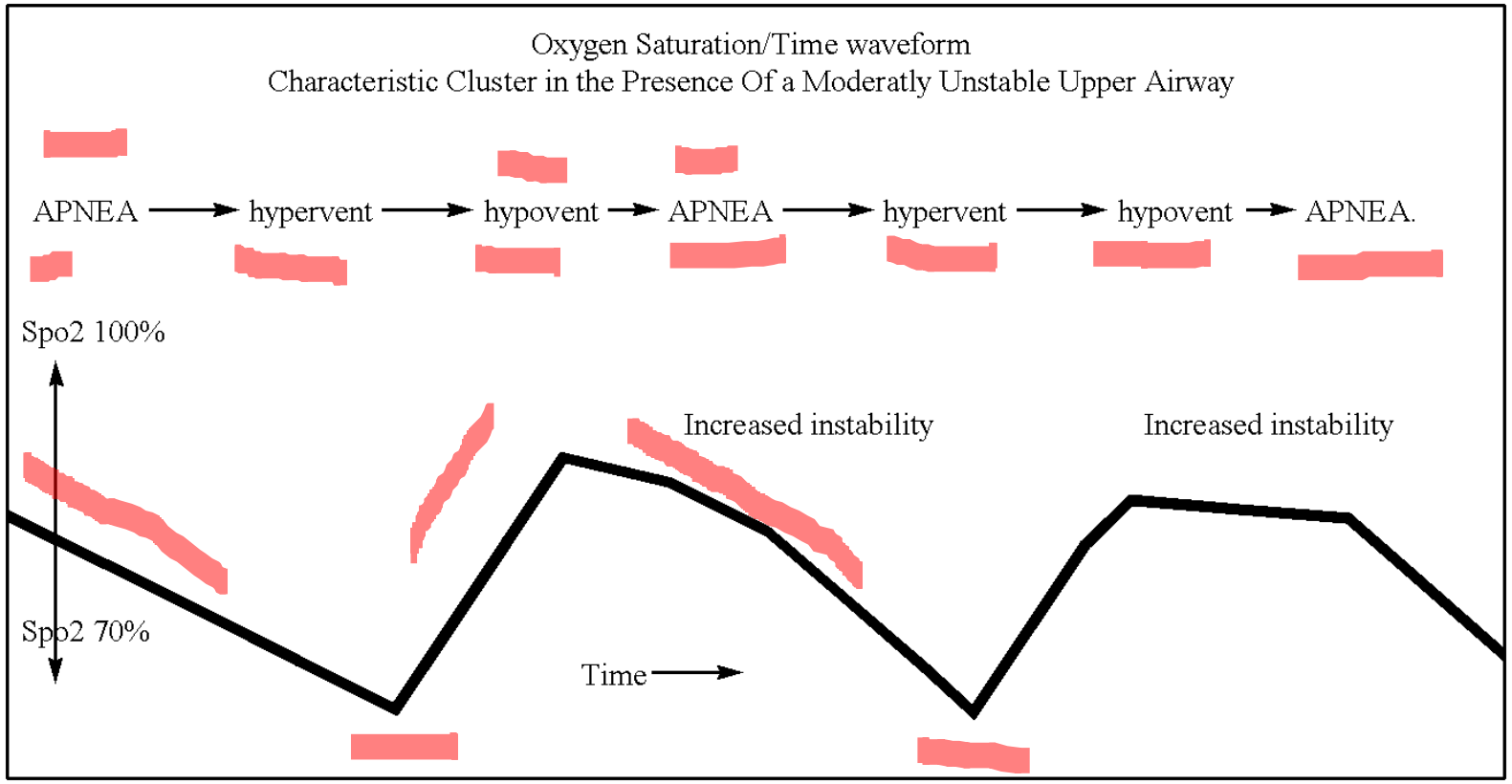
Those and other findings about sleep are common knowledge among scientists today thanks to Don Chisholm, Mary Ellen Havel-Lang, Paul Minkus and more than

Wisconsin Sleep Cohort Study.

The UW School of Medicine and Public Health study, of state workers who periodically undergo sleep tests at UW Hospital and provide other information, has continued for 23 years.

Rasmuson prepares Chisholm for an overnight sleep evaluation. A 23-year study of more than 1,540 state workers has revealed higher rates of cancer and death for people with sleep apnea. "You are asleep for a third of your life," said Terry Young, a lead researcher of the study. "Abnormalities are bound to have an

Apnea Vs Spo2



Hypertension and Snoring

The Nurses' Health Study

- *Snorers versus non-snorers*

- 1986 study for 8 years
- 72,231 Nurses aged 40-65
- Increase risk of 1.6 for the development of hypertension over an 8-year

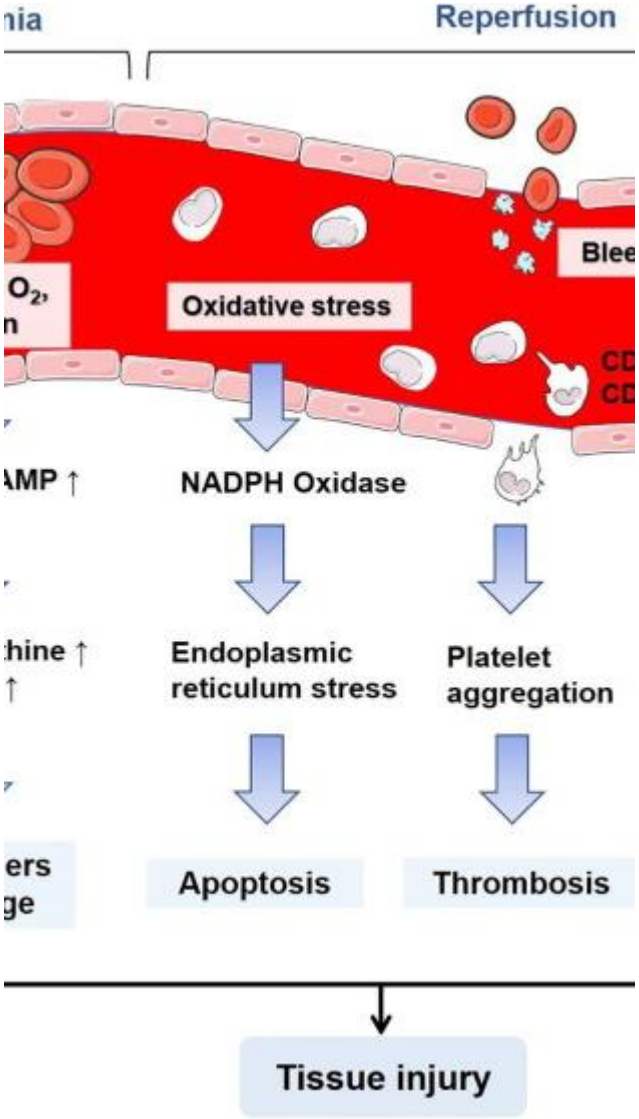
Possible mechanisms linking Sleep Apnea to Cardiovascular consequences

Repetitive hypercapnic/ hypoxia events

Repetitive reoxygenation and oxygen form free radicals

Stimulate a sympathetic response (“fight or flight response”, “stress” response)

Inhibition of parasympathetic tone



Ischemia-Reperfusion Injury

Ischemia–reperfusion associated with thrombolytic therapy, organ transplantation, coronary angioplasty, aortic cross-clamping, or cardiopulmonary bypass results in local and systemic inflammation

Paradoxical exacerbation of cellular dysfunction and death, following restoration of blood flow to previously ischemic tissues

Reactive oxygen species have a destructive role in mediating tissue damage during IRI.

During ischemia, the degradation of ATP produces hypoxanthine.

Once the ischemic tissue is reperfused, an influx of molecular oxygen catalyses xanthine oxidase to degrade hypoxanthine to uric acid and thereby liberating the highly reactive superoxide anion.

Superoxide is subsequently converted to hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH^{\bullet}$).

OSA and Oxidative Stress

Apnea-

- Multiple cycles of hypoxia/ reoxygenation inducing oxidative stress or free radicals' formation
- Free radicals damage cellular functions
  - Activates inflammatory/immune responses
  - Facilitates endothelial cell injury and dysfunction
  - Atherosclerosis and other cardiovascular morbidities

Oxidative stress is also a crucial component of obesity and metabolic disorders such as Dyslipidemia , Type 2 diabetes, and Metabolic syndrome

What is Oxidative Stress?

Imbalance between oxidant-producing systems and antioxidants

Superoxide and Superoxide dismutase

Cellular respirations of the mitochondria is mostly responsible for free radicals with superoxide being the leader

Leads to interruption of essential physiologic signaling

Also damages various cell structures such as membranes, lipids, proteins, and DNA

Reaction of superoxide with the powerful vasodilator nitric oxide (NO), which promotes the formation of peroxynitrite while diminishing the bioactivity and bioavailability of NO.

This activity is a major contributor of oxidative/nitrosative stress in the vasculature, hence, greatly affecting endothelial function, vascular inflammation, and atherosclerosis.


CHD, Cardiac Fibrosis, Hypertension, Ischemia, Myocardial infarction
Heart
Macular degeneration, Retinal degeneration, Cataracts
Eyes
Skin Aging, Sunburn, Psoriasis, Dermatitis, Melanoma
Skin
Diabetes, Ageing, Chronic Fatigue
Multi-Organ
Free Radical Oxidative Stress
Chronic Kidney disease, Renal Graft, Nephritis
Kidney
Restenosis, Atherosclerosis, Endothelial Dysfunction, Hypertension
Blood Vessels
Rheumatoid, Osteoarthritis, Psoriasis
Joints
Immune System
Lung
Brain
Chronic Inflammations, Auto-immune disorders, Lupus, IBD, MS, Cancer
Asthma, COPD, Allergies, ARDS, Cancer
Alzheimer, Parkinson OCD, ADHD, Autism, Migraine, Stroke, Trauma, Cancer

Oxidative Stress in OSA

Hypoxia/reoxygenation triggers mitochondrial dysfunction

- 200% to 300% increase in free radical's levels with OSA

Endothelial dysfunction

- Reaction of superoxide with nitric oxide (NO) reduces the bioavailability of NO
- Leads to vascular inflammation and atherosclerosis

To reduce free radical production the body synthesizes:

- Xanthine oxidase
- Endothelial NO synthase

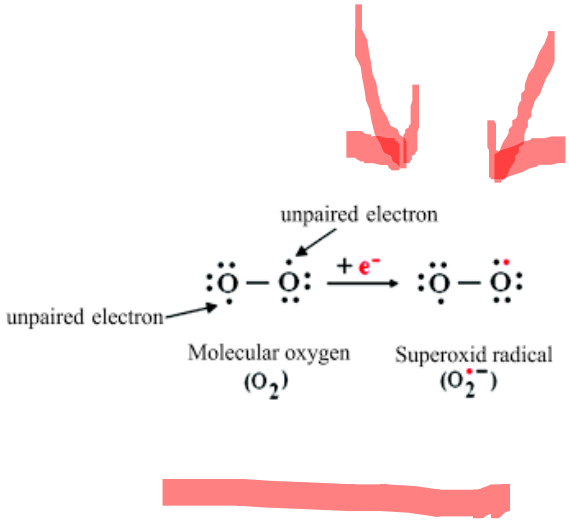
Did you know that treatment nCPAP reduces free radical production?

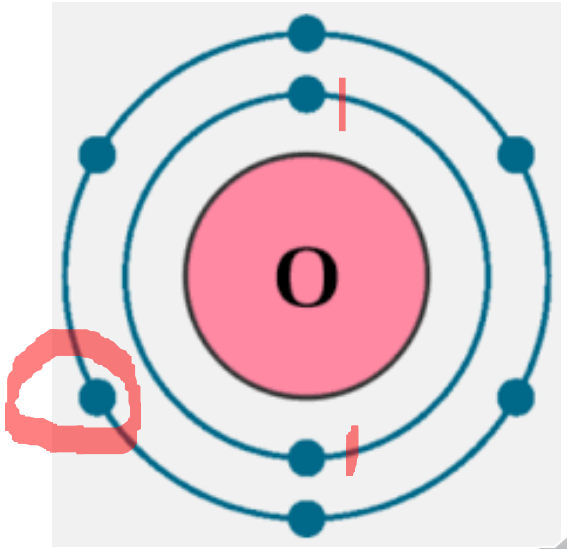
Common free radicals

Generated by reduction of molecular oxygen

Three main free radicals

- Superoxide- most abundant
- Hydrogen peroxide
- Hydroxyl radical



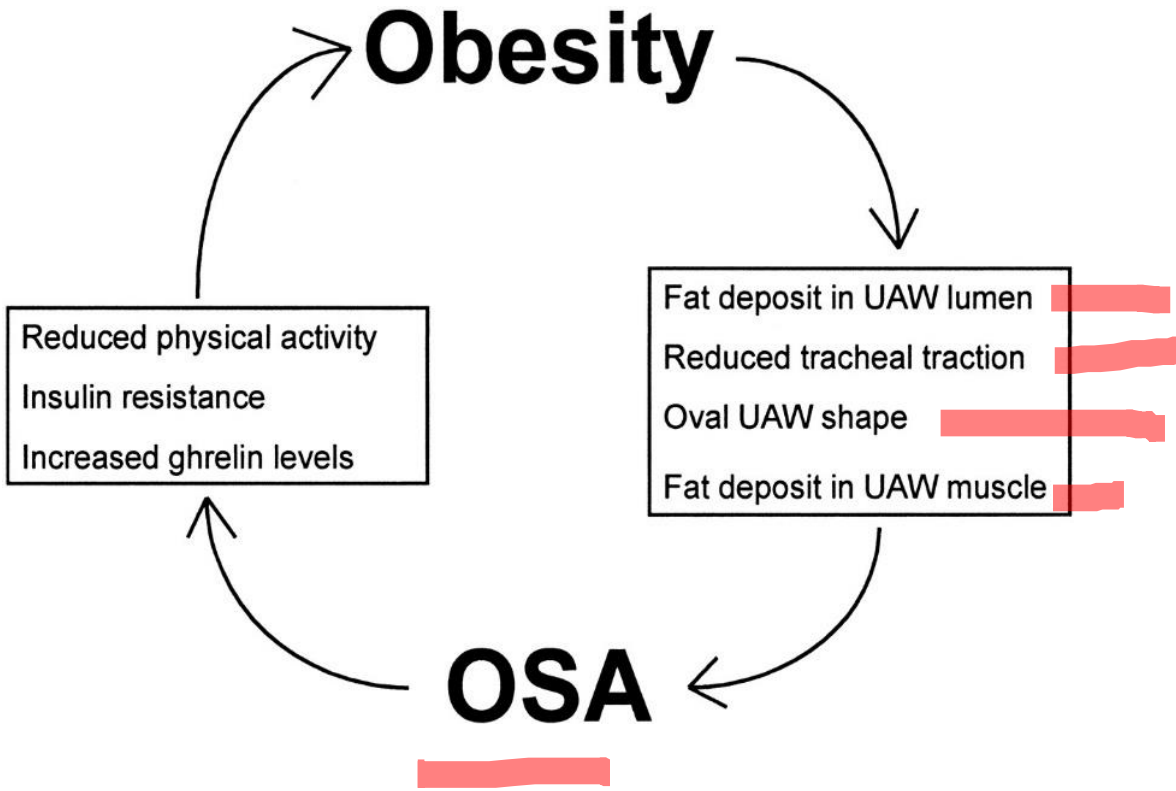


Obesity and OSA

Obesity is one of the major cardiovascular risk factors associated with OSA

60% to 90% of OSA patients are obese

Weight aggravates the severity of OSA



Syndrome Z

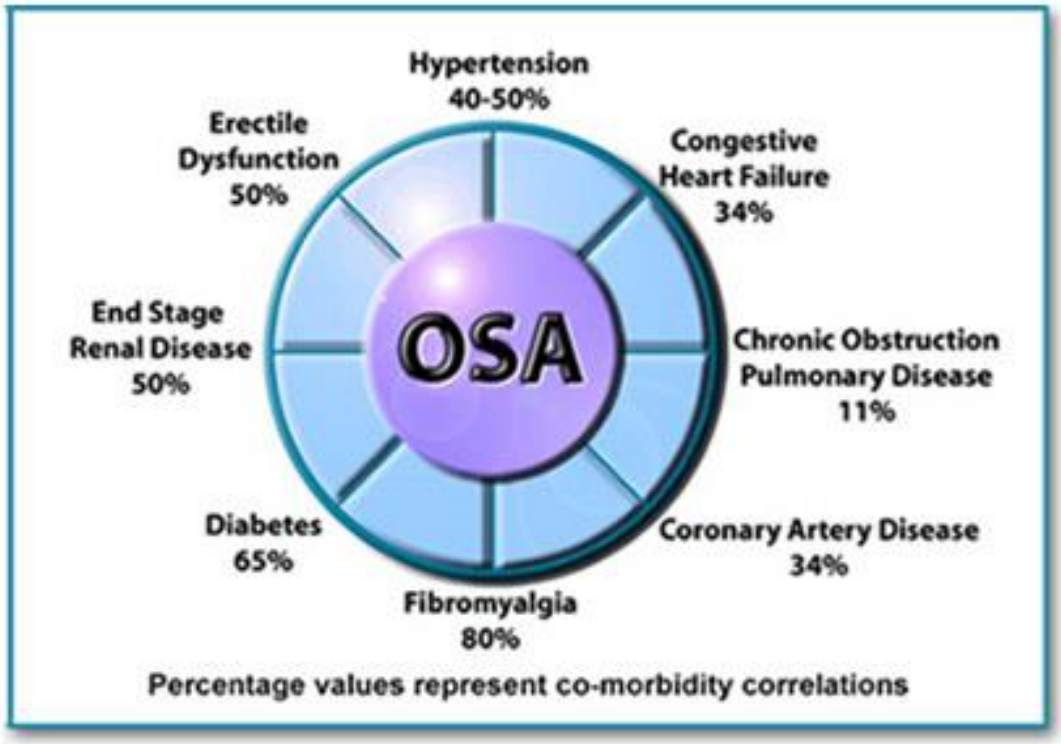
Describes the interaction of obstructive sleep apnea (OSA) with vascular risk factors:

- Hypertension
- Central obesity
- Insulin resistance and hyperlipidemia
- Metabolic syndrome

Obesity and metabolic syndrome

Oxidative stress correlated with BMI in many studies

- Highly associated with systemic oxidative stress markers
- BMI >30 most at risk
- Fat accumulation was closely correlated with markers of systemic oxidative stress
- Plasma adiponectin levels were inversely correlated with oxidative stress



Oxidative Stress in Obesity

Oxidative stress leads to inflammation and atherosclerosis

Metabolic syndrome

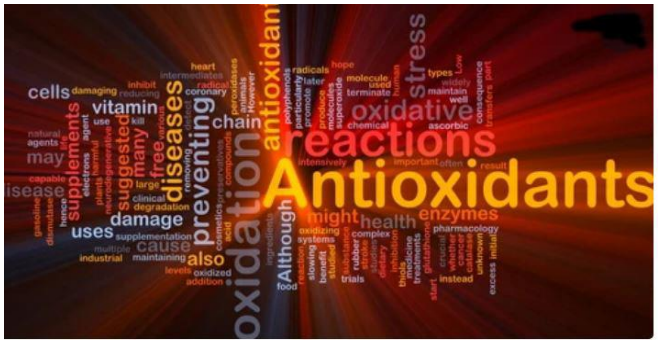
- Hyperglycemia
- Dyslipidemia
- Hypertension and obesity
  - Risk factors for inflammation and atherosclerosis

Oxidative stress may contribute to diabetes

- Impair glucose uptake in muscle and fat
- Decrease insulin secretion from pancreatic beta cells

Hyperglycemia was also shown to trigger increased formation of ROS and oxidative stress via glucose autooxidation, mitochondrial dysfunction, NADPH oxidase, and a variety of oxidant-producing enzymes

Hyperglycemia was also shown to trigger increased formation of free radicals and oxidative stress



Increased oxidative stress also underlies the pathophysiology of

- Hypertension
- Hyperlipidemia
- Insulin resistance
- Obesity

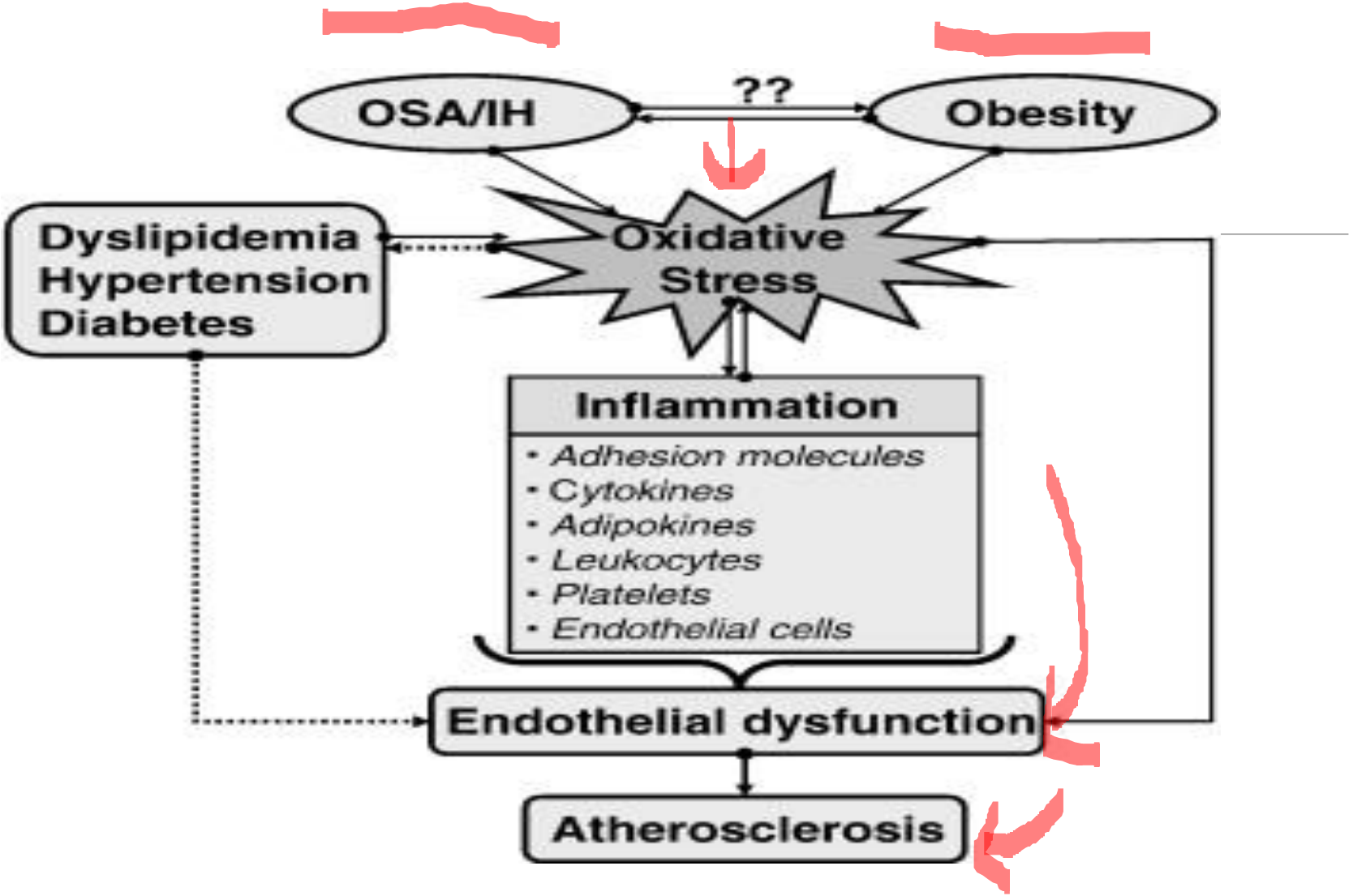
Insulin Resistance and Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is present in about 30% of the OSA patients

Diabetes mellitus in snorers was higher than nonsnorers particularly in the obese patients

Dependent on sleep apnea severity measures such as apnea-hypopnea index (AHI) and minimum oxygen saturation

Treatment with nCPAP immediately restored blood glucose levels

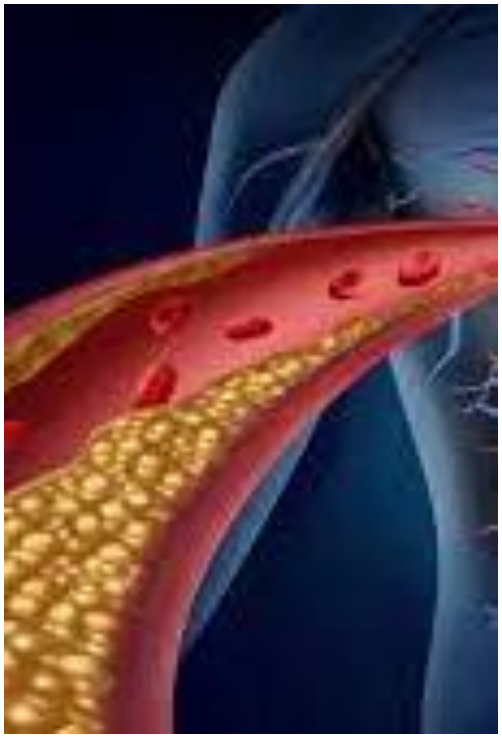

OSA/IH
??
Obesity
Dyslipidemia
Hypertension
Diabetes
Oxidative Stress
Inflammation
• Adhesion molecules
• Cytokines
• Adipokines
• Leukocytes
• Platelets
• Endothelial cells
Endothelial dysfunction
Atherosclerosis

Dyslipidemia and OSA

Sleep Heart Health Study

Dyslipidemia is also a prevalent finding among patients with sleep apnea

- Increase cholesterol and triglycerides
- Decreased HDL's
- Dysfunctional HDL and lower antioxidant activity of paraoxonase 1 bound to HDL, has been detected in patients with OSA
- **nCPAP treatment lowered serum total cholesterol levels**



Cardiovascular morbidity and sleep apnea

Association of sleep apnea and cardiovascular disease is overwhelming

Several studies also demonstrated that sleep apnea syndrome is an independent risk factor for cardiovascular mortality

- 50% of the sleep apnea patient are hypertensive
- 10% to 15% have history of MI

Hypertension

Epidemiological studies have shown that approximately 40% of patients with sleep apnea have hypertension

OSA and Hypertension-Why does it happen?

Repetitive changes in oxygen saturations and large swings in intrathoracic pressures have been implicated

Changes are detected by receptors in the brain and in the periphery (carotid bodies)

Stimulate a sympathetic response (“fight or flight response”, “stress” response)

Leads to increased heart rate and blood pressure

Risk Factors for Hypertension

More common and more severe in African Americans

Increased salt intake

Excess alcohol intake

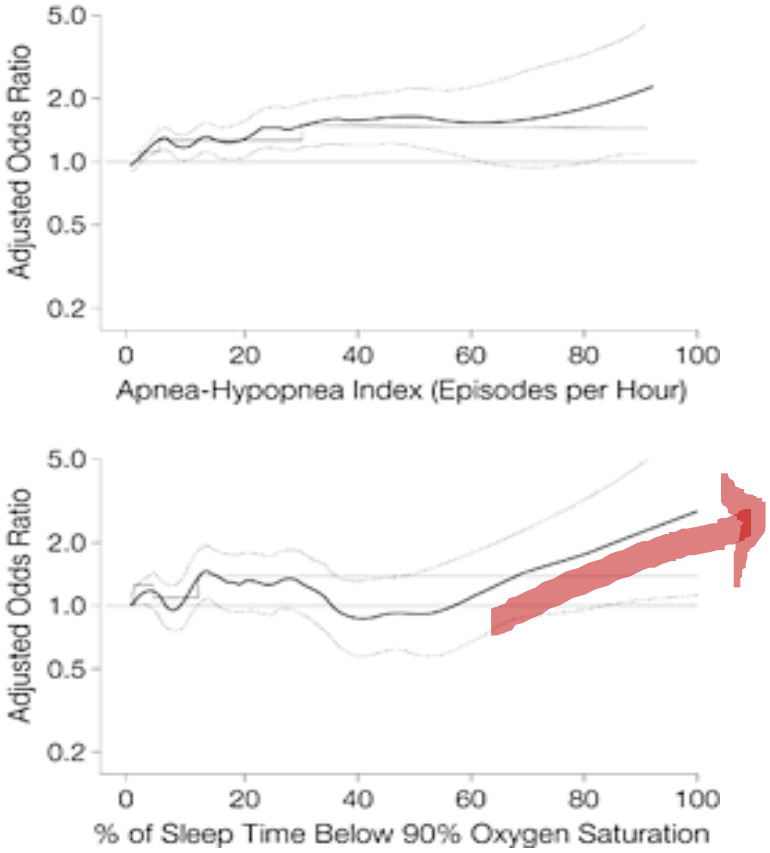
High cholesterol also has been associated with the development of hypertension

Hypertension may be more common among those with certain personality traits, such as hostile attitudes and time urgency/impatience

The Relationship between Obstructive Sleep Apnea and Hypertension

Odds of having hypertension is 37% greater in OSA

Odds of having hypertension is 46% greater in those who Spo2 is less than 90% with OSA



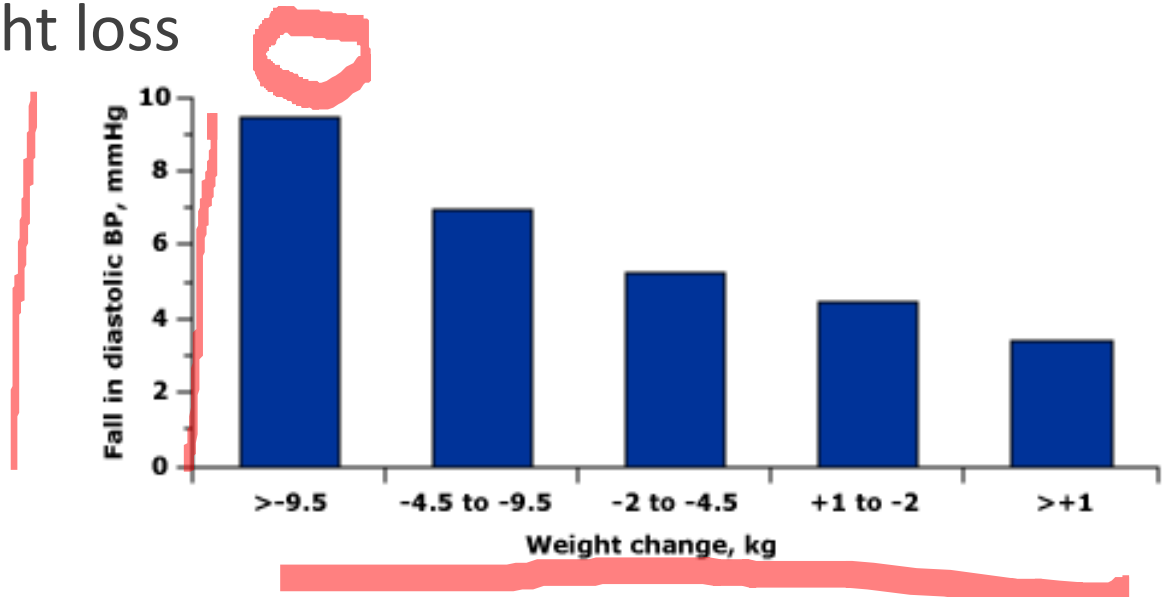
Nieto, F. J. et al. JAMA 2000;283:1829-1836

Obesity and Hypertension

Obesity is associated with an increased risk of hypertension

Weight loss improves blood pressure

The chart below shows the fall in diastolic pressures with weight loss



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Concluding Remarks

Oxidative stress and consequently systemic inflammation are by now recognized as fundamental mechanisms in the pathophysiology of cardiovascular morbidity in OSA

nCPAP has been shown to improve all aspects of OSA and oxidative stress

The best remedy may be a combination of weight loss, exercise, and using nCPAP

Further research is being done on antioxidant therapy

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