Obstructive Sleep Apnea and Metabolic Syndrome: Where is the Chicken? Where is the Egg?

Vsevolod Y. Polotsky, MD, PhD

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Obstructive Sleep Apnea and Metabolic Syndrome: Where is the Chicken? Where is the Egg?

Vsevolod Y. Polotsky, M.D., Ph.D.
Associate Professor of Medicine
Division of Pulmonary and Critical Care Medicine,
Johns Hopkins University School of Medicine, Baltimore, MD, USA

November 5, 2014
DISCLOSURE

• No financial relationships with commercial entities to disclose
• I will not reference an unlabeled/unapproved use of a drug or product in my presentation.
Intermittent Hypoxia

Transthoracic Pressure Swings

Sleep Fragmentation

Hypercapnea
PREVALENCE

AHI ≥ 5: 24% in men and 9% in women
(Young et al., 1993)

30-60% in obese individuals
(Vgontzas, 2000; Punjabi 2002; Young 1993 and 2002; Tufik 2010)
Sleep-Disordered Breathing and Mortality: a Prospective Cohort Study

Current evidence suggests that increased cardiovascular risk of OSA may be related to the increased prevalence of the metabolic syndrome in patients with OSA.
Current evidence suggests that increased cardiovascular risk of OSA may be related to the increased prevalence of the metabolic syndrome in patients with OSA.
Metabolic Syndrome (NCEP, 2001 and AHA/NHLBI, 2004) Any 3 of the following

- Abdominal obesity
- Serum triglycerides > 150 mg/dl
- HDL-C < 40 mg/dl in men and < 50 mg/dl in women
- BP > 130/85 (or treated for HTN)
- Fasting blood glucose > 100 mg/dl (or Medx)

+ Non-alcoholic fatty liver disease
• Obstructive Sleep Apnea, Insulin Resistance and Type 2 Diabetes

• Obstructive Sleep Apnea and Dysregulation of Lipid Metabolism

• Obstructive Sleep Apnea and Fatty Liver
• Obstructive Sleep Apnea, Insulin Resistance and Type 2 Diabetes

• Obstructive Sleep Apnea and Dysregulation of Lipid Metabolism

• Obstructive Sleep Apnea and Fatty Liver
Obstructive Sleep Apnea Is Independently Associated with Insulin Resistance

MARY S. M. IP, BING LAM, MATTHEW M. T. NG, WAH KIT LAM, KENNETH W. T. TSANG, and KAREN S. L. LAM
Am J Respir Crit Care Med Vol 165. pp 670–676, 2002

Sleep-disordered Breathing and Insulin Resistance in Middle-aged and Overweight Men

NARESH M. PUNJABI, JOHN D. SORKIN, LESLIE I. KATZEL, ANDREW P. GOLDBERG, ALAN R. SCHWARTZ, and PHILIP L. SMITH
Am J Respir Crit Care Med Vol 165. pp 677–682, 2002
HOMA = $G_0 \times l_0 / 22.5$

Prevalence of OSA in T2DM
CPAP effect

• 9 small RCT (1 – 12 wks)
• in different population of apneics

• Different outcomes (SI, HbA1C, fasting blood glucose and insulin)

• 4 studies showed some improvement , 5 showed none
CPAP effect

Chirinos et al.

CPAP effect

New data from Punjabi and Tasali presented at ATS 2014 indicate significant improvement of insulin resistance with CPAP
What are the mechanisms?
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Intermittent Hypoxia

- Transthoracic Pressure Swings
- Sleep Fragmentation
- Hypercapnea
Mouse Model of Intermittent Hypoxia
Intermittent Hypoxia is a Complex Stimulus: IH Events Fragment Sleep

Mouse Model of Intermittent Hypoxia

Intermittent Hypoxia Increases Insulin Resistance and Suppresses Insulin Secretion

Mouse Model of Intermittent Hypoxia

Systemic Effects (Carotid bodies, SNS)

Liver
Muscle
Epididymal fat

Carotid Body governs systemic responses to Intermittent Hypoxia
Carotid Sinus Nerve Dissection
Carotid Body governs systemic responses to Intermittent Hypoxia

Changes in mean arterial blood pressure in controls and rats exposed to episodic hypoxia for sham-operated and carotid-body-denervated (CBD) rats on going from baseline to final measurement. Values are means ± SEM. *P<0.05, versus group control and baseline.

Carotid Sinus Nerve Dissection (CSND) prevents IH-induced fasting hyperglycemia

Carotid Sinus Nerve Dissection (CSND) prevents an IH-induced increase in hepatic glucose output (hyperinsulinemic euglycemic clamp)

A.
Baseline hepatic glucose output (µmol/kg/min)

B.
Whole body glucose flux during the clamp (µmol/kg/min)

Carotid Sinus Nerve Dissection (CSND) prevents an IH-induced increase in gluconeogenesis

CSND abolishes sympathetic activation in the liver

Carotid Body Governs Systemic Responses to Intermittent Hypoxia

Intermittent Hypoxia

Carotid Body

Brainstem

Sympathetic Nervous System

↑ Epinephrine Efflux by Adrenal Medulla

↓ Pancreatic Insulin Secretion

↑ Lipolysis

↑ Hepatic Glucose Output

↑ Adipose Tissue FFA

↓ Muscle Insulin Resistance
• Obstructive Sleep Apnea, Insulin Resistance and Type 2 Diabetes

• Obstructive Sleep Apnea and Dysregulation of Lipid Metabolism

• Obstructive Sleep Apnea and Fatty Liver
OSA is Associated with Dyslipidemia

| TABLE 5. Cholesterol, HDL cholesterol, and triglycerides by quartiles of RDI* in SHHS* participants at risk for incident CVD* (n = 4,991), United States, October 1995 to February 1998 |
|--------------------------------------------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                                  | RDI                           | 0-<1.25         | 1.25-<4.0       | 4.0-<10.7       | ≥10.7-115.6     | Overall         | F test (general) | Trend           |
| Cholesterol (mg/dl; mean (SD))                   |                                |                 |                 |                 |                 |                 |                 |                 |
| Men                                              |                                |                 |                 |                 |                 |                 |                 |                 |
| <65 years                                        | 197.2 (37.2)                  | 202.8 (39.3)    | 204.9 (40.3)    | 206.0 (37.8)    | 203.4 (38.8)    | 0.043           | 0.0078          |
| ≥65 years                                        | 196.3 (32.4)                  | 194.4 (36.0)    | 198.3 (39.7)    | 200.4 (35.1)    | 198.1 (36.4)    | 0.312           | 0.0984          |
| Women                                            |                                |                 |                 |                 |                 |                 |                 |                 |
| <65 years                                        | 203.8 (40.9)                  | 209.3 (39.8)    | 210.6 (38.8)    | 205.8 (37.4)    | 206.8 (39.6)    | 0.052           | 0.1272          |
| ≥65 years                                        | 214.0 (38.3)                  | 217.9 (35.9)    | 215.8 (39.2)    | 211.6 (32.3)    | 215.1 (36.7)    | 0.239           | 0.397           |
| HDL cholesterol (mg/dl; mean (SD))               |                                |                 |                 |                 |                 |                 |                 |                 |
| Men                                              |                                |                 |                 |                 |                 |                 |                 |                 |
| <65 years                                        | 46.7 (14.5)                   | 42.8 (11.9)     | 42.7 (12.6)     | 41.0 (12.3)     | 42.8 (12.8)     | <0.0001         | <0.0001         |
| ≥65 years                                        | 47.0 (14.0)                   | 44.6 (11.2)     | 44.9 (11.4)     | 45.3 (13.2)     | 45.3 (12.4)     | 0.4544          | 0.5425          |
| Women                                            |                                |                 |                 |                 |                 |                 |                 |                 |
| <65 years                                        | 57.7 (16.8)                   | 55.1 (15.8)     | 51.2 (15.4)     | 49.0 (16.7)     | 54.6 (16.6)     | <0.0001         | <0.0001         |
| ≥65 years                                        | 60.0 (17.1)                   | 57.5 (15.9)     | 55.6 (14.7)     | 54.4 (14.8)     | 56.9 (15.8)     | 0.0006          | <0.0001         |
| Triglycerides (mg/dl; mean (SD))                 |                                |                 |                 |                 |                 |                 |                 |                 |
| Men                                              |                                |                 |                 |                 |                 |                 |                 |                 |
| <65 years                                        | 155.6 (139.4)                 | 158.8 (114.9)   | 166.2 (160.4)   | 178.9 (131.2)   | 163.4 (136.6)   | 0.0023          | 0.0002          |
| ≥65 years                                        | 125.1 (65.5)                  | 146.5 (85.5)    | 137.5 (72.5)    | 144.5 (88.2)    | 140.5 (81.0)    | 0.1068          | 0.1424          |
| Women                                            |                                |                 |                 |                 |                 |                 |                 |                 |
| <65 years                                        | 128.5 (83.9)                  | 136.1 (76.8)    | 163.1 (125.4)   | 164.9 (95.6)    | 142.2 (94.4)    | <0.0001         | 0.0001          |
| ≥65 years                                        | 136.3 (69.1)                  | 147.6 (88.2)    | 152.0 (100.2)   | 152.9 (88.6)    | 147.2 (87.8)    | 0.1325          | 0.0305          |

CPAP and Plasma Lipids: Randomized Studies

<table>
<thead>
<tr>
<th></th>
<th>Therapeutic CPAP</th>
<th>Subtherapeutic CPAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0 (SD)</td>
<td>Day 30 change (CI)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/dl</td>
<td>220 (43)</td>
<td>-10.8 (-17.4 to -4.2)</td>
</tr>
<tr>
<td>mmol/l</td>
<td>5.7 (1.1)</td>
<td>-0.28 (-0.45 to -0.11)</td>
</tr>
<tr>
<td>Tryglicerides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/dl</td>
<td>230 (168)</td>
<td>-21.2 (-24.8 to 67.3)</td>
</tr>
<tr>
<td>mmol/l</td>
<td>2.6 (1.9)</td>
<td>-0.24 (-0.28 to 0.76)</td>
</tr>
</tbody>
</table>

Circulating cardiovascular risk factors in obstructive sleep apnoea: data from randomised controlled trials

G V Robinson, J C T Pepperell, H C Segal, R J O Davies, J R Stradling

Independent Association Between Nocturnal Intermittent Hypoxemia and Metabolic Dyslipidemia in Obstructive Sleep Apnea

CPAP (2 months) and Postprandial Plasma Lipids: a Cross-over Randomized Placebo-Controlled Study

i has a cheezie
Intermittent Hypoxia increases VLDL levels

CIH for 12 weeks in C57BL/6J mice

Intermittent Hypoxia and Adipose Tissue Lipolysis
Mouse Model of Intermittent Hypoxia

Systemic Effects (Carotid bodies, SNS)
Lipolysis in Adipose Tissue

Kathy Jaworski, Eszter Sarkadi-Nagy, Robin E. Duncan, Maryam Ahmadian and Hei Sook Sul

Intermittent Hypoxia induces lipolysis via the carotid body and downstream sympathetic efferent pathways.

In patients with sleep apnea nocturnal elevation of plasma FFA levels is caused by IH

Intermittent Hypoxia and Lipoprotein Clearance
Mouse Model of Intermittent Hypoxia

Tissue Specific Effects (Hypoxia inducible factors, etc)
Intermittent Hypoxia Decreases Chylomicron Clearance

VLDL Lipid Biosynthesis

LPL Hydrolysis

CO₂ + H₂O β-Oxidation

CM

LPL

TG

CM LPL

VLDL

LDL

TG
Intermittent Hypoxia Decreases Lipoprotein Lipase (LpL) Activity in Adipose Tissue

Angiopoietin-like Protein 4 Rapidly Inactivates Lipoprotein Lipase (LPL)

Intermittent Hypoxia Increases Adipose Angptl4

![Graph showing changes in Angptl4 mRNA fold change across different tissues (Epididymal Fat, Skeletal Muscle, Heart) with CIA and CIH conditions.](image)

Angptl4 Ab prevent CIH-induced dyslipidemia

Drager, Yao et al. AJRCCM 2013; 188:240-8
Angptl4 Ab prevent CIH-induced atherosclerosis

Drager, Yao et al. AJRCCM 2013; 188:240-8
In obese patients, expression of Angptl4 in subcutaneous fat depended on the severity of hypoxemia and OSA.

Drager, Yao et al. AJRCCM 2013; 188:240-8
Interruption Hypoxia and Lipoprotein Clearance

- ↓ Lipoprotein clearance by up-regulating adipose Angptl4, a potent inhibitor of lipoprotein lipase
- Adipose tissue hypoxia may play a role in cardiovascular morbidity and mortality of OSA
• OSA and Intermittent Hypoxia

• Intermittent Hypoxia, Insulin Resistance and Type 2 Diabetes

• Intermittent Hypoxia and Dysregulation of Lipid Metabolism

• Intermittent Hypoxia and Fatty Liver
Non-alcoholic fatty liver disease

- Fatty liver
- Inflammation, fibrosis
- Cirrhosis
## OSA and Non-Alcoholic Fatty Liver

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 NAFLD by histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aron-Wisnewsky 2012</td>
<td>8.3%</td>
<td>2.96 [1.13, 7.73]</td>
<td></td>
</tr>
<tr>
<td>Campos 2008</td>
<td>7.4%</td>
<td>4.00 [1.33, 12.07]</td>
<td></td>
</tr>
<tr>
<td>Daltro 2010</td>
<td>3.5%</td>
<td>1.84 [0.31, 10.91]</td>
<td></td>
</tr>
<tr>
<td>Jouet 2007</td>
<td>4.3%</td>
<td>0.60 [0.07, 5.39]</td>
<td></td>
</tr>
<tr>
<td>Kallwitz 2007</td>
<td>0.9%</td>
<td>3.14 [0.12, 79.39]</td>
<td></td>
</tr>
<tr>
<td>Polotsky 2009</td>
<td>1.6%</td>
<td>3.67 [0.47, 28.40]</td>
<td></td>
</tr>
<tr>
<td>Tannè 2005</td>
<td>0.8%</td>
<td>10.00 [0.85, 117.02]</td>
<td></td>
</tr>
<tr>
<td>Ulitsky 2010</td>
<td>39.9%</td>
<td>1.36 [0.78, 2.35]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>66.7%</td>
<td>2.01 [1.36, 2.97]</td>
<td></td>
</tr>
</tbody>
</table>
OSA and Non-Alcoholic Fatty Liver

Polotsky et al. Am J Respir Crit Care Med, 179 (2009), pp. 228–234
### OSA and Non-Alcoholic Fatty Liver: Liver Fibrosis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>M-H, Fixed, 95% CI</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aron-Wisnewsky 2012</td>
<td>11.4%</td>
<td>1.04 [0.06, 17.43]</td>
<td></td>
</tr>
<tr>
<td>Campos 2008</td>
<td>24.1%</td>
<td>1.85 [0.34, 10.05]</td>
<td></td>
</tr>
<tr>
<td>Daltro 2010</td>
<td>4.9%</td>
<td>3.46 [0.12, 100.51]</td>
<td></td>
</tr>
<tr>
<td>Jouet 2007</td>
<td>5.8%</td>
<td>3.00 [0.17, 51.75]</td>
<td></td>
</tr>
<tr>
<td>Kallwitz 2007</td>
<td>8.8%</td>
<td>3.00 [0.24, 36.88]</td>
<td></td>
</tr>
<tr>
<td>Mishra 2008</td>
<td>11.0%</td>
<td>5.80 [0.66, 51.19]</td>
<td></td>
</tr>
<tr>
<td>Polotsky 2009</td>
<td>4.7%</td>
<td>3.00 [0.09, 102.05]</td>
<td></td>
</tr>
<tr>
<td>Sundaram 2012</td>
<td>12.1%</td>
<td>2.00 [0.19, 20.61]</td>
<td></td>
</tr>
<tr>
<td>Tanné 2005</td>
<td>6.0%</td>
<td>2.29 [0.08, 66.02]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

| 100.0% | 2.68 [1.23, 5.82] |

---

G. Musso¹, M. Cassader², C. Olivetti¹, F. Rosina¹, G. Carbone¹ and R. Gambino²

*obesity* reviews (2013) 14, 417–431
i has a checzie
Intermittent Hypoxia Causes Steatohepatitis and Liver Fibrosis
What are the mechanisms?
Lysyl oxidase (LOX)

- Secreted amine oxidase.
- Catalyzes formation of covalent bonds between collagen fibers.
- Tissue hypoxia (via HIF-1) increases expression of LOX.

Kagan et al., 2003.
Erler et al., 2006; Higgins et al., 2007.
Mouse Model of Intermittent Hypoxia

Tissue Specific Effects (Hypoxia inducible factors, etc)
Intermittent hypoxia up-regulates collagen cross-linking enzyme lysyl oxidase in hepatocytes via hypoxia inducible factor $1 \alpha$.

**In vivo**

Liver LOX mRNA (fold change)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>IH</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>HIF1α+/-</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

**In vitro**

<table>
<thead>
<tr>
<th></th>
<th>16% O₂</th>
<th>1% O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HIF1α+/-</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Mesarwi et al. Manuscript in preparation*
LOX secreted by hepatocytes in hypoxic cross-links collagen
LOX secreted by hepatocytes in hypoxic cross-links collagen

Mesarwi et al. Manuscript in preparation
Study design

• 35 consecutive patients recruited from the Bariatric Surgery clinic at Johns Hopkins Bayview Medical Center.
• Polysomnogram
• Serum LOX checked the morning after PSG.
• Liver biopsies analyzed for steatosis, fibrosis, and NAFLD activity score.
• Patients categorized by presence/absence of hepatic fibrosis.
OSA → IH → LOX → Liver Fibrosis

\[ R = 0.51, \ p < 0.002 \]

Mesarwi et al. Manuscript in preparation
OSA $\rightarrow$ IH $\rightarrow$ LOX $\rightarrow$ Liver Fibrosis

Mesarwi et al. Manuscript in preparation
Mechanisms of Liver Fibrosis during IH: Hypothesis

1. IH induces liver tissue hypoxia

2. Liver tissue hypoxia up-regulates HIF-1α

3. HIF-1α up-regulates LOX

4. LOX cross-links collagen resulting in liver fibrosis
Current Members of the Laboratory

Dr. Jonathan Jun  Dr. Mi-Kyung Shin  Ms. Shannon Bevans-Fonti
Dr. Qiaoling Yao  Dr. Omar Mesarwi

Formers Members of the Laboratory

Dr. David Li  Dr. Luciano Drager  Dr. Christian Reinke
Dr. Vladimir Savransky  Ms. Ashika Nanayakkara-Bind

JHU Collaborators
Alan R Schwartz, MD
Philip L. Smith, MD
Susheel P Patil, MD, PhD
Naresh M. Punjabi, MD, PhD
Gregg L Semenza MD, PhD
Machiko Shirahata, PhD
Annabelle Rodriguez, PhD
Ann Moser, BS
Kimberley Steele, MD
Michael Schweitzer, MD

University of Maryland
Carole Sztalryd, PhD

Columbia University
William Blaner, PhD

UT Southwestern
Philipp Scherer PhD.

Lexicon Inc
David Powell, PhD

NIH: HL080105, HL068715, P50 HL084945, AHA: 10GRNT3360001
ResMed Foundation