

Pathogenesis of Metabolic Dysfunction in Sleep Apnea: The Role of Sleep Fragmentation and Intermittent Hypoxemia

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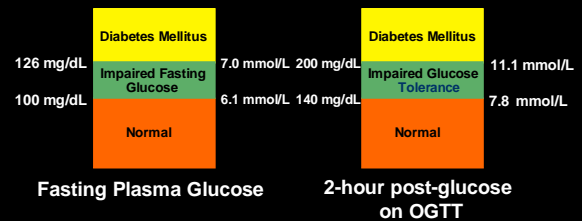
General Outline

- Definition and Epidemiology:
 - Metabolic Dysfunction and Sleep Apnea
- Background: Sleep Apnea and Metabolic Dysfunction
- Effects of Intermittent Hypoxia on Glucose Metabolism
- Effects of Sleep Fragmentation on Glucose Metabolism

General Outline

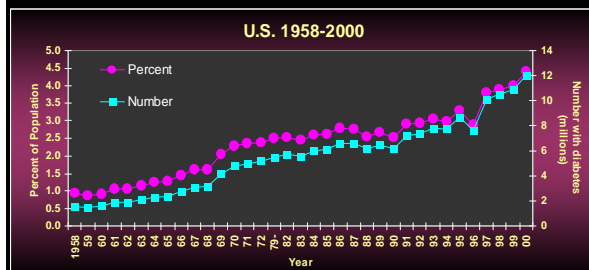
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Disease Definition: Metabolic Dysfunction Diabetes and Glucose Tolerance



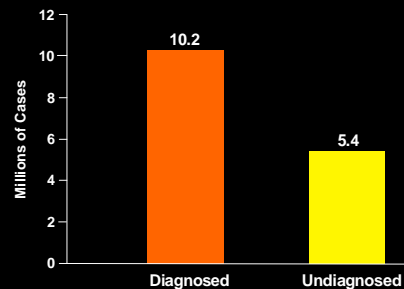
Adapted from The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.
Diabetes Care, 2004.

Prevalence of Diabetes in the US

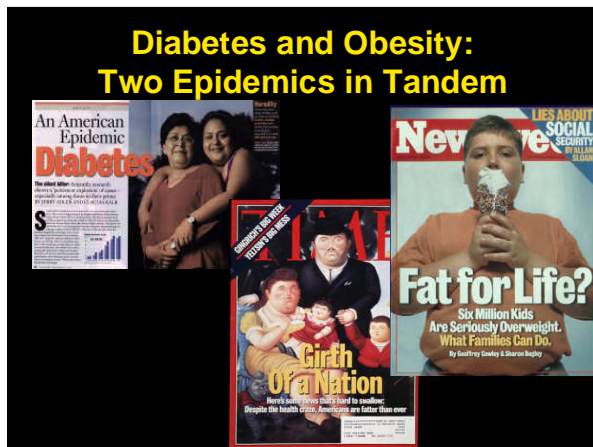
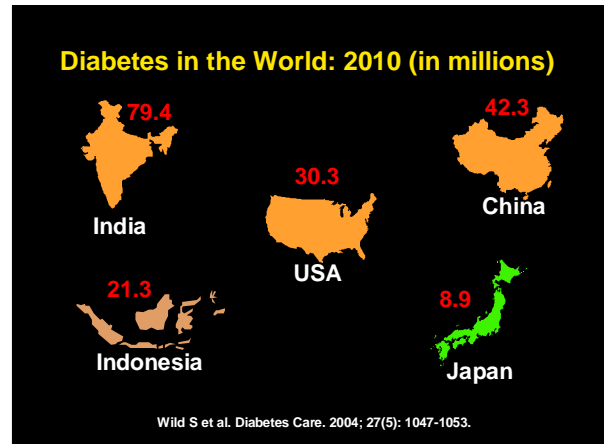
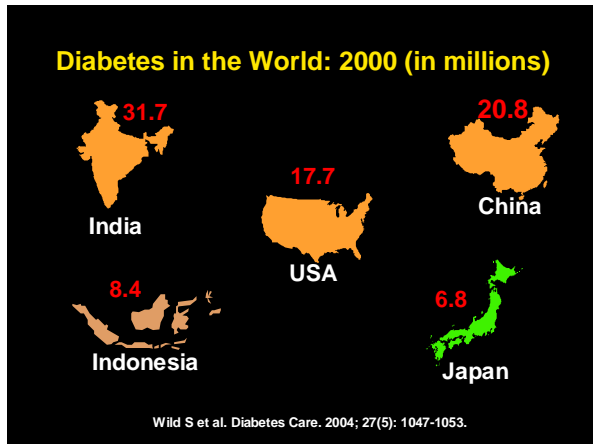


Center for Disease Control (Division of Diabetes, 2003)

Diagnosed and Undiagnosed Diabetes (US) Estimated Cases Among Adults, 1997

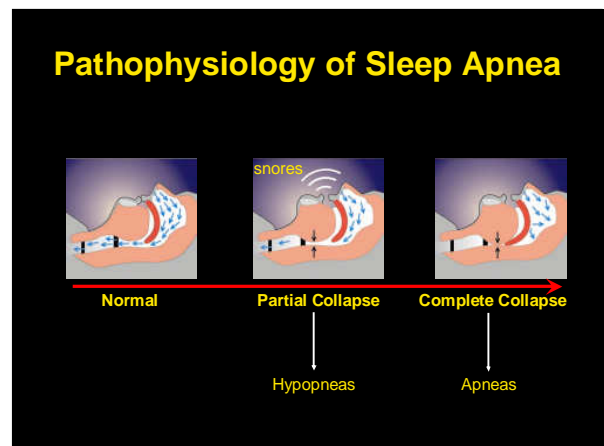


Harris, et al. *Diabetes Care*, 1998;21:518-24.

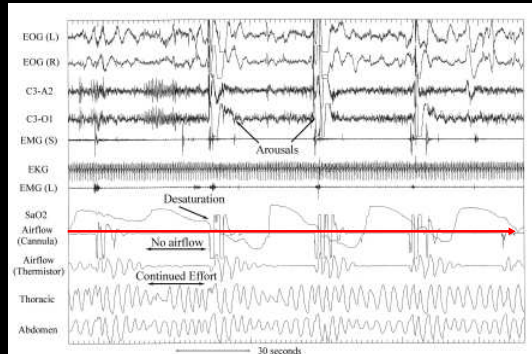


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- ### Definition of the Disorder: Sleep Apnea
- Terminology:
 - Obstructive sleep apnea (OSA)
 - Sleep apnea (SA)
 - Sleep apnea-hypopnea syndrome (SAS)
 - Sleep-disordered breathing (SDB)



Tracing of Obstructive Apneas



Definition of the Disorder

- Disease Defining Metric:
 - Apnea-Hypopnea Index (AHI)
 - = Number of apneas and hypopneas per hour of sleep
 - Respiratory Disturbance Index (RDI)
 - "Normal": AHI or RDI < 5 events / hour

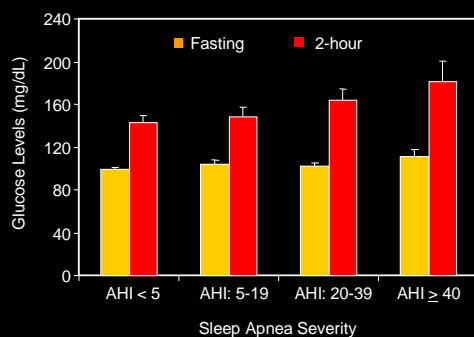
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Sleep Apnea and Glucose Tolerance

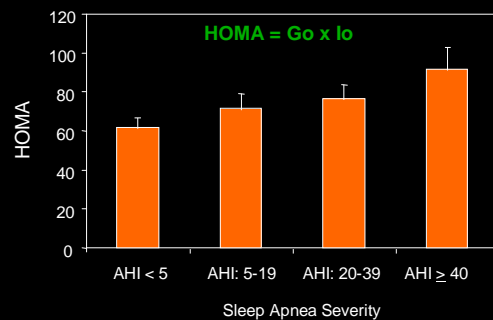
- Study Design
 - > Community-based cohort study
 - > 150 healthy but overweight men
 - > No history of diabetes (normal glucose)
 - > No cardiovascular or pulmonary disease
 - > Normal stress test (Bruce Protocol)

Sleep Apnea and Glucose Tolerance



Punjabi et al. AJRCCM. 2002

Sleep Apnea and Insulin Resistance



Punjabi et al. AJRCCM. 2002

Obstructive Sleep Apnea Is Independently Associated with Insulin Resistance

MARY S. M. IP, BING LIAM, MATTHEW M. T. NG, WAH KIT LAM, KENNETH W. T. TSANG, and KAREN S. L. LAM
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong S.A.S., PR China

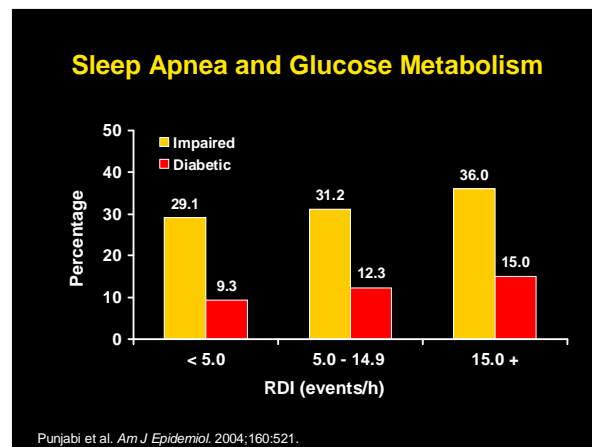
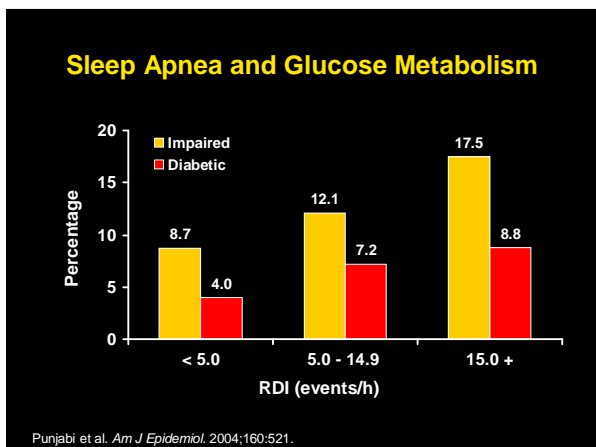
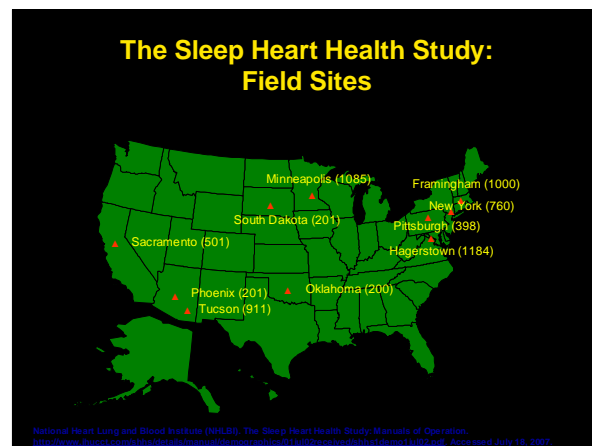
TABLE 4. STEPWISE MULTIPLE LINEAR REGRESSION MODELS FOR HOMA-IR

| | Model 1 (n = 10,466) | | Model 2 (n = 10,466) | |
|------------------------|----------------------|---------|------------------------|---------|
| | Estimate ± SE | p Value | Estimate ± SE | p Value |
| R ² = 26.5% | | | R ² = 26.6% | |
| BMI, kg/m ² | 0.071 ± 0.010 | < 0.001 | 0.047 ± 0.017 | 0.005 |
| AHI, events/h | 0.005 ± 0.002 | 0.044 | 0.014 ± 0.006 | 0.024 |
| R ² = 26.5% | | | R ² = 26.5% | |
| BMI, kg/m ² | 0.070 ± 0.010 | < 0.001 | 0.070 ± 0.010 | < 0.001 |
| MIH, % | -0.002 ± 0.004 | 0.022 | -0.002 ± 0.004 | 0.022 |

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index.
Other independent variables: AHI, time with oxygen saturation < 90%, and 4-hour oxygen saturation (%HbO₂), recent sleep, age, sex, and smoking.

Ip et al. *AJRCM*. 2002

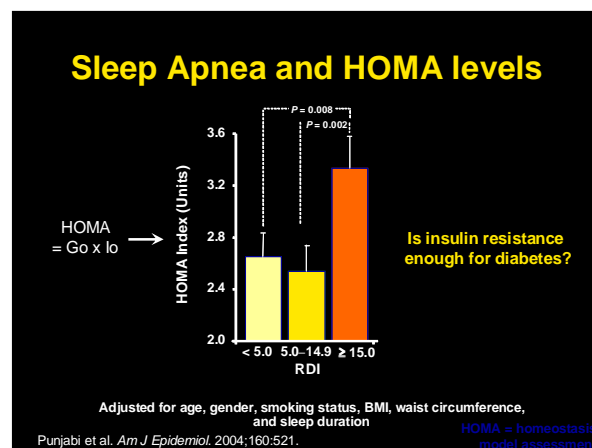
Are there population data?



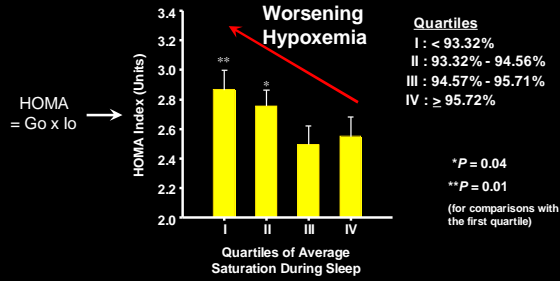
Sleep Apnea and Glucose Metabolism

| Predictor | Fasting Glucose Level (n = 2,656) | |
|---|-----------------------------------|-------------|
| | Odds Ratio | 95% CI |
| Respiratory disturbance index (no. of events/hour) | | |
| < 5.0 | 1.00 | |
| 5.0 - 14.9 | 1.27 | 0.98 - 1.64 |
| ≥ 15.0 | 1.46 | 1.09 - 1.97 |
| Average oxyhemoglobin saturation during sleep (%) | | |
| ≥ 95.72 | 1.00 | |
| 94.57 - 95.71 | 1.52 | 1.05 - 2.20 |
| 93.32 - 94.56 | 1.75 | 1.21 - 2.53 |
| < 93.32 | 1.95 | 1.34 - 2.84 |

Punjabi et al. *Am J Epidemiol*. 2004;160:521.

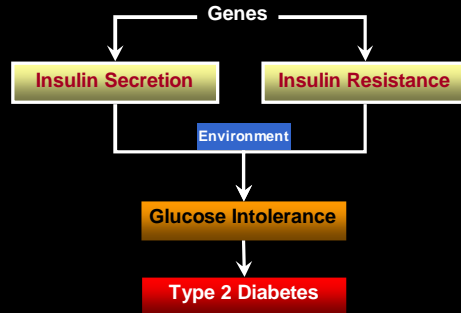


Sleep Apnea and Metabolic Dysfunction: HOMA and Oxygen Saturation

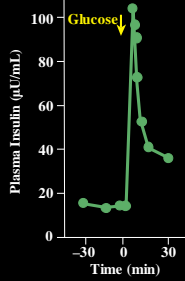


Punjabi et al. *Am J Epidemiol.* 2004;160:521.

Glucose Intolerance and Diabetes: Two Defects

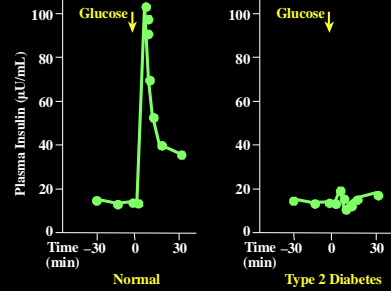


Acute Insulin Response to IV Glucose: Normal Subjects



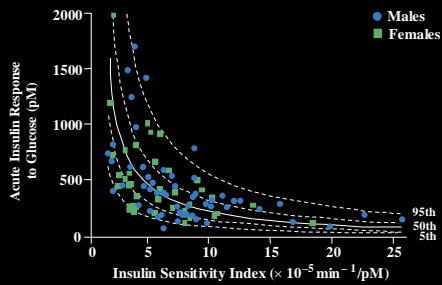
Adapted from Robertson & Porte. *J Clin Invest.* 1973;52:870-876, with permission.

Acute Insulin Response to IV Glucose: Normal and Type 2 Diabetic Subjects



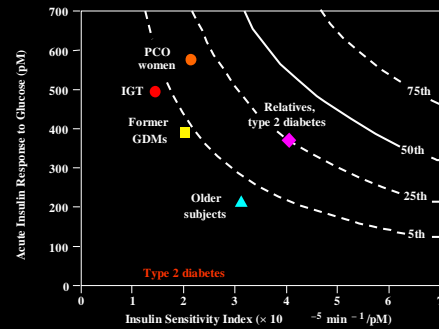
Adapted from Robertson & Porte. *J Clin Invest.* 1973;52:870-876, with permission.

Insulin Secretion: Modulation by Insulin Sensitivity

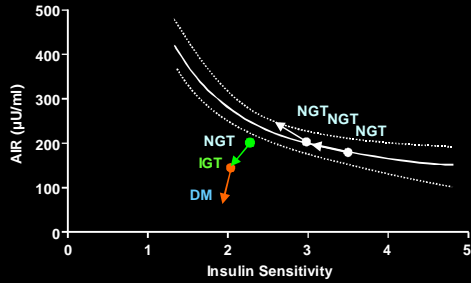


Adapted from Kahn, et al. *Diabetes.* 1993;42:1663-1672, with permission

Insulin Sensitivity and Insulin Secretion: Relationship in Type 2 Diabetes and Groups at Risk



Changes in acute insulin response (AIR) relative to changes in Insulin Sensitivity



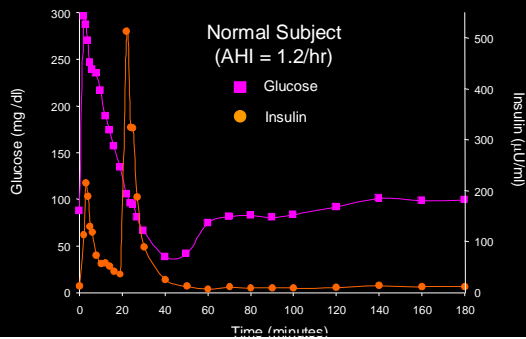
Weyer C et al. J Clin Invest 1999;104:787-794

Insulin Sensitivity and Insulin Secretion in Sleep Apnea

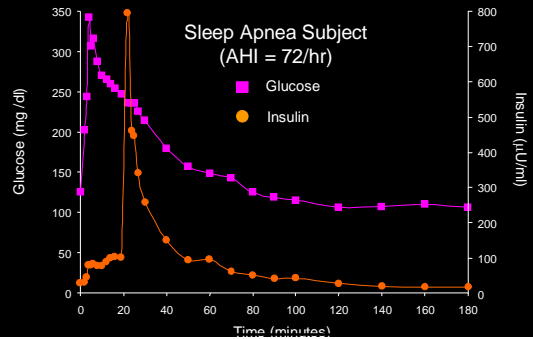
- 118 subjects (no medical conditions)
- Men 71 and Women 47
- Predominantly white (86.4%)
- Mean age was 45.7 years (range: 23 – 73)
- Mean BMI was 29.4 kg/m² (range: 17.2 – 52.2).

Punjabi et al. ARJCCM, 2008; In press

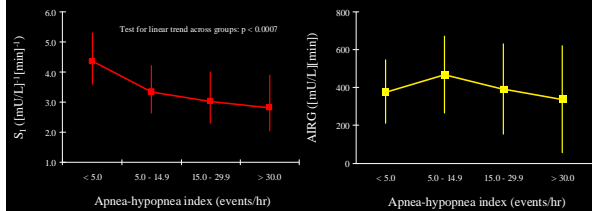
Insulin and Glucose Profile: IVGTT



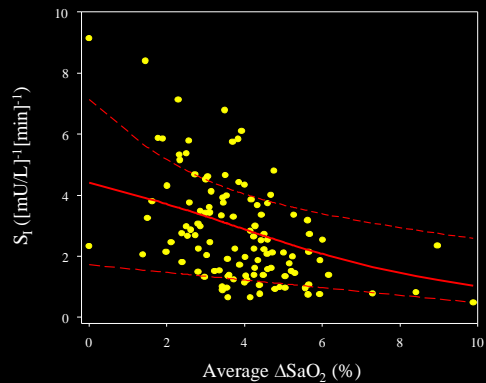
Insulin and Glucose Profile: IVGTT



Insulin Sensitivity and Insulin Secretion Effects of Sleep Apnea



Insulin Sensitivity and Oxygen Desaturation



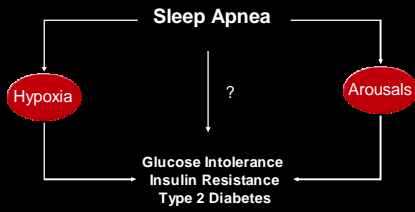
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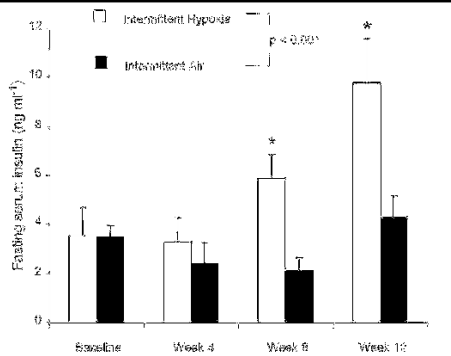
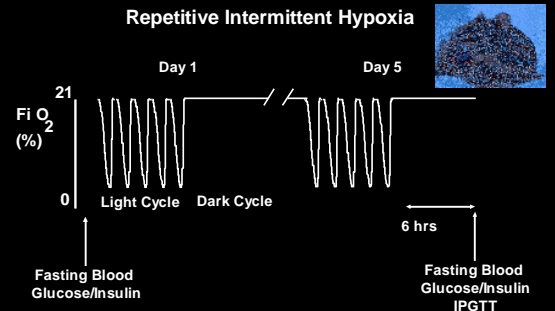
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Pathogenesis of Metabolic Dysfunction



Animal Experiment



Intermittent hypoxia increases insulin levels
Intermittent hypoxia worsens insulin sensitivity

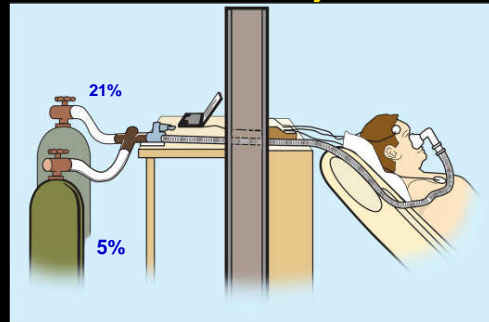
Human Experimental Approach

- Two distinct experimental paradigms
 - Effects of acute intermittent hypoxia in normal subjects
 - 5-hour exposure during wakefulness
 - Effects of sleep fragmentation in normal subjects
 - Two nights of sleep disruption with auditory and mechanical stimuli (~60/hr)

Human Experimental Approach

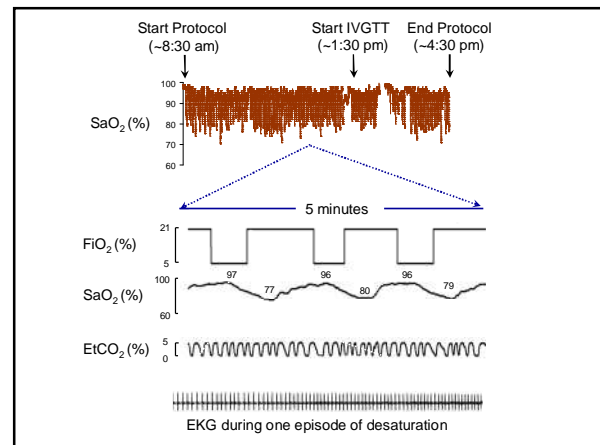
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Acute Intermittent Hypoxia in Normal Subjects

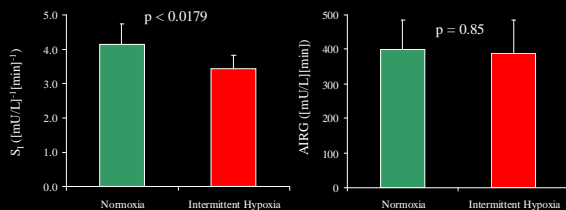


Acute Intermittent Hypoxia in Normal Subjects

- Study Protocol
 - Hypoxia day
 - 5% O₂ continued until O₂ saturation reaches 85%
 - 21% O₂ continued until O₂ saturation reaches baseline level (95-97%)
 - Normoxia day
 - 21% O₂ delivered throughout the 8-hour period
 - Manual two-way valve used to alternate from one room air tank to another



Insulin Sensitivity and Insulin Secretion Effects of Hypoxia in Normal Subjects

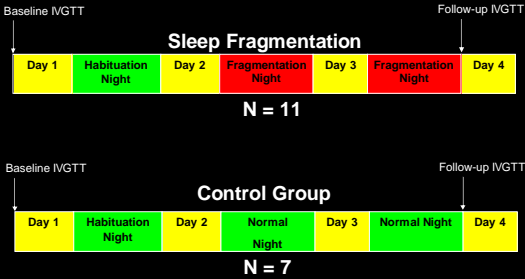


Intermittent Hypoxia is associated with decrease in insulin sensitivity but without a compensatory increase in insulin secretion

Human Experimental Approach

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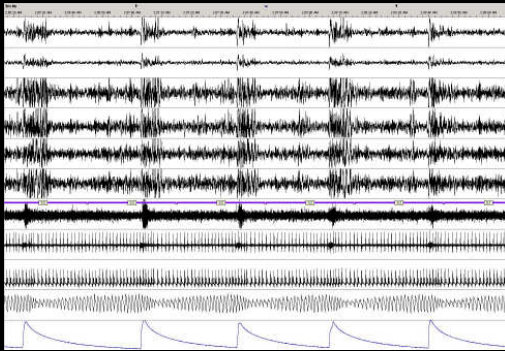
Sleep Fragmentation in Normal Subjects



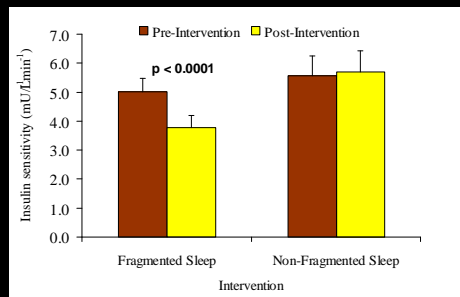
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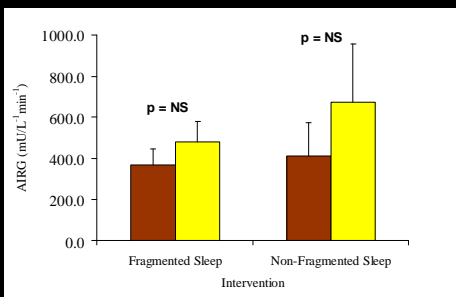
Sleep Fragmentation in Normal Subjects



Insulin Sensitivity with Fragmented Sleep



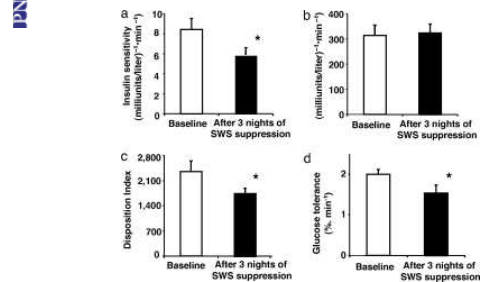
Insulin Secretion with Fragmented Sleep

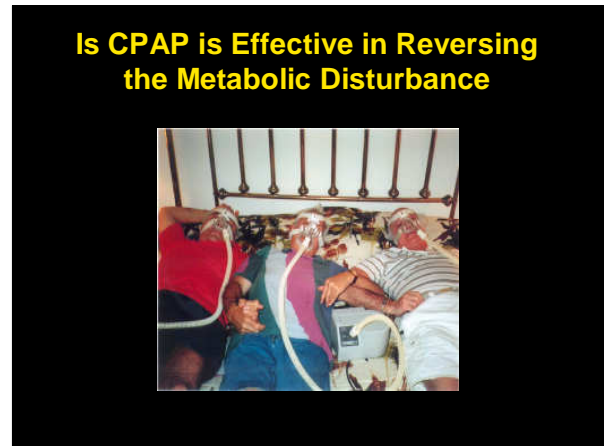
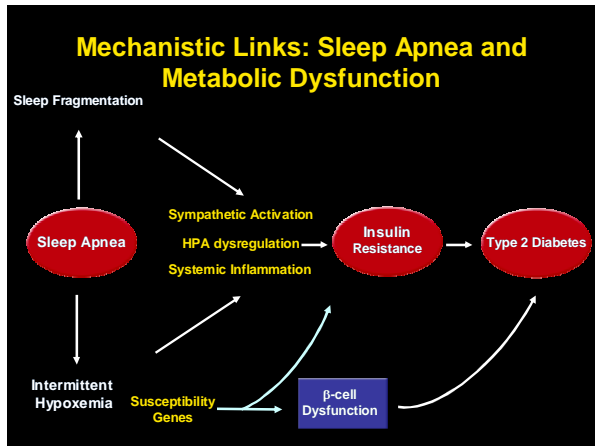


Slow-wave sleep and the risk of type 2 diabetes in humans

Eze Tsafiri¹, Rachel Leporell, David A. Ehrman, and Eze Van Caster

Tasali E. et al. PNAS 2008;105:1044-1049



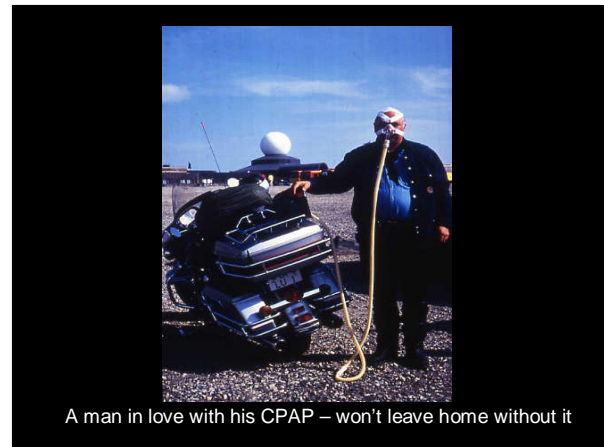


Effects of CPAP on Insulin Sensitivity

Insulin Sensitivity Index (ISI) assessed with the hyperinsulinemic clamp at baseline, after 2 d, and after 3 m of CPAP therapy

| | ISI (Whole group, n = 40) (After 3 months, n = 31) ($\mu\text{mol/kg} \cdot \text{min}$) |
|----------------------------------|--|
| Baseline | 5.75 \pm 4.20 |
| After 2 days CPAP therapy | 6.79 \pm 4.91 |
| Improvement compared to baseline | $P = 0.003$ |
| After 3 months CPAP therapy | 7.54 \pm 4.84 |
| Improvement compared to baseline | $P = 0.001$ |

Harsch et al. *Am J Respir Crit Care Med.* 2004;169:156.



- ### Conclusions and Summary
- Independent of obesity, sleep apnea is associated with insulin resistance, glucose intolerance, and type 2 diabetes
 - Intermittent hypoxemia and recurrent arousals may mediate the metabolic abnormalities in sleep apnea
 - CPAP appears to mitigate the metabolic disturbance? (more research is still needed)

