
# News Release

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**Press conference time: May 18, 11:15 a.m. in the ATS Press Room (E-1)**

Poster session time: 8:15- 10:45 a.m. May 17
Location: CC-Room 395-396 (Third Level), Morial Convention Center

## Sleep Apnea May Increase Insulin Resistance

Sleep apnea may cause metabolic changes that increase insulin resistance, according to researchers from the University of Pittsburgh Medical Center. The intermittent hypoxia associated with sleep apnea causes a distinct drop in insulin sensitivity in mice, even though chronic hypoxia, such as that associated with high altitude, did not.

The research will be reported at the ATS 2010 International Conference in New Orleans.

To determine whether intermittent hypoxia (IH) and chronic hypoxia (CH) would have different metabolic effects, Dr. Lee and colleagues fitted adult male mice with arterial and venous catheters for continuous rapid blood monitoring of glucose and insulin sensitivity. They then exposed the mice to either seven hours of IH, in which treatment, oxygen levels oscillated, reaching a low of about 5 percent once a minute, or CH, in which they were exposed to oxygen at a constant rate of 10 percent, and compared each treatment group to protocol-matched controls.

When compared to the control group, the IH mice demonstrated impaired glucose tolerance and reduced insulin sensitivity; the CH group, however, showed only a reduction in glucose tolerance but not insulin sensitivity compared to controls. “Both intermittent hypoxia and continuous hypoxia exposed mice exhibited impaired glucose tolerance, but only the intermittent hypoxia exposed animals demonstrated a reduction in insulin sensitivity,” said Euhan John Lee, M.D., a

fellow at the Medical Center.

“The intermittent hypoxia of sleep apnea and the continuous hypoxia of altitude are conditions of hypoxic stress that are known to modulate glucose and insulin homeostasis. Although both forms of hypoxia worsen glucose tolerance, this research demonstrated that the increase in insulin resistance that accompanies intermittent hypoxia, or sleep apnea, is greater than that seen with continuous hypoxia, or altitude,” explained Dr. Lee.

The specific finding that intermittent, but not continuous, hypoxia induced insulin resistance was not expected.

Increased generation of reactive oxygen species, initiation of pro-inflammatory pathways, elevated sympathetic activity, or upregulation of insulin counter-regulatory hormones in IH may contribute to the greater development of insulin resistance in those mice versus those exposed to continuous hypoxia.

“As sleep apnea continues to rise with the rate of obesity, it will be increasingly important to understand both the independent and interactive effects of both morbidities on the development of metabolic disorders. This research demonstrated that intermittent hypoxic exposure can cause changes in insulin sensitivity and insulin secretion, which may have important consequences in metabolically vulnerable diabetic patients who present with co-morbid sleep apnea,” said Dr. Lee. “Future research will explore potential inflammatory and lipotoxic pathways by which intermittent hypoxia disrupts glucose and insulin homeostasis.”

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“Intermittent Hypoxia (IH) Causes Insulin Resistance and Impaired Insulin Secretion in C57BL/6J Mice” (Session B19, Monday, May 17, 8:15-10:45 a.m., CC-Room 395-396 (Third Level), Morial Convention Center; Abstract 2110)

**Please note that numbers in this release may differ slightly from those in the abstract. Many of these investigations are ongoing; the release represents the most up-to-date data available at press time.*

# Intermittent hypoxia (IH) causes insulin resistance and impaired insulin secretion in C57BL/6J mice

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INTRODUCTION: Intermittent hypoxia (IH) as a result of obstructive sleep apnea (OSA) is associated with impaired glucose tolerance and decreased insulin sensitivity. Although there is mounting evidence to suggest a direct physiologic link between IH and metabolic dysfunction that is independent of obesity, the mechanisms are not well understood. We developed the first frequently sampled intravenous glucose tolerance test (FSIVGTT) in conscious mice to examine the effects of IH and chronic hypoxia (CH) on glucose disposal.

METHODS: Adult male C57BL/6J mice with chronic femoral artery and venous catheters were exposed to seven hours of either IH (nadir inspired oxygen 5-6% at 60 cycles $hr^{-1}$) or CH (constant 10% oxygen). Control groups were exposed to either intermittent air (IA) or were unhandled (UH). FSIVGTT was performed during the last two hours of exposure by rapidly sampling arterial blood for glucose and (insulin) at (–10), (0), (1), (2), 3, (4), 5, 6, (8), 10, (12), 14, (16), 18, (20), 25, (30), 40, 50, (60), (90), and (120) min, with a bolus of intravenous dextrose (1 g/kg) given at time 0. Data analysis was performed in collaboration with the Bergman group at USC, utilizing the previously validated Minimal Model program (SI = insulin sensitivity, Sg = glucose effectiveness, AIRg = acute insulin response to glucose, DI = disposition index, AUCglucose = area under the curve for glucose over 120 minutes).

RESULTS: The IH group, when compared to matched IA control group, demonstrated impaired glucose tolerance and reduced SI, Sg and AIRg. The CH group, compared to UH matched control group, also demonstrated impaired glucose tolerance and reduced Sg and AIRg, but no change in SI. There were no significant differences in any parameters between the IH and CH groups, or between the IA and UH groups. * $p<0.05$ IH vs. IA control; # $p<0.05$ CH vs. UH control.

FSIVGTT and Minimal Model Outcomes

| | Intermittent Air | Intermittent Hypoxia | Unhandled | Chronic Hypoxia |
|---|---|---|---|---|
| AUCglucose (mg/dl*min) | 14796±814 | 21000±1189* | 13824±527 | 19929±821# |
| SI (uU/ml/min) | 16.90±5.32 | 7.50±2.68* | 19.90±5.14 | 13.90±4.06 |
| Sg (1/min)*$10^{-2}$ | 0.088±0.011 | 0.039±0.180* | 0.127±0.190 | 0.051±0.007# |
| AIRg (uU/ml.min) | 175.2±41.0 | 91.2±18.2* | 200.7±32.1 | 116.9±16.3# |

| | | | | |
|---|---|---|---|---|
| Disposition Index | 3046±1214 | 786±352 | 3607±770 | 1817±735 |

CONCLUSION: As shown through the FSIVGTT and minimal model, both IH and CH cause impaired glucose tolerance through a reduction in Sg and AIRg, with IH also causing a reduction in SI.