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

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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.

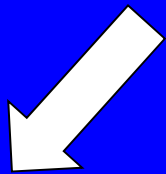
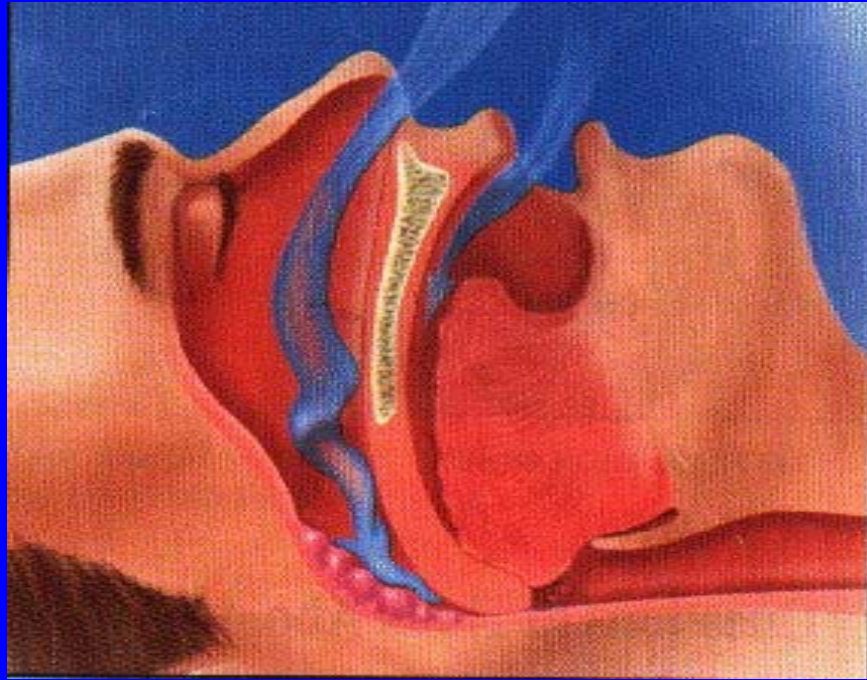
Associate Professor of Medicine

**Division of Pulmonary and Critical Care Medicine,
Johns Hopkins University School of Medicine, Baltimore,
MD, USA**

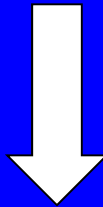
November 5, 2014

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.**



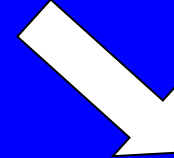
**Intermittent
Hypoxia**



**Transthoracic
Pressure
Swings**

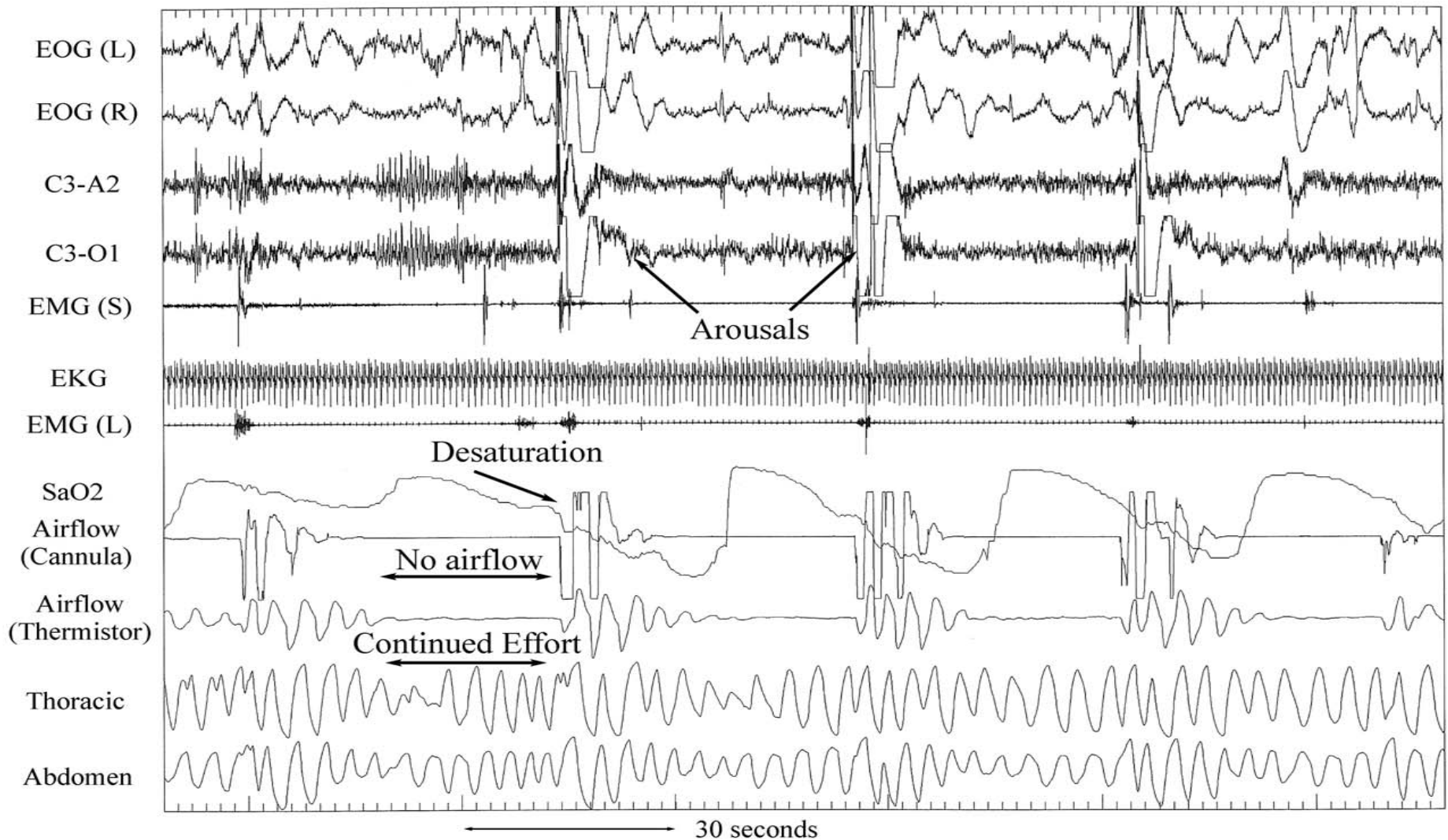


**Sleep
Fragmentation**



Hypercapnea

TRACING OF OBSTRUCTIVE APNEAS DURING SLEEP



PREVALENCE

AHI \geq 5: 24% in men and 9% in women

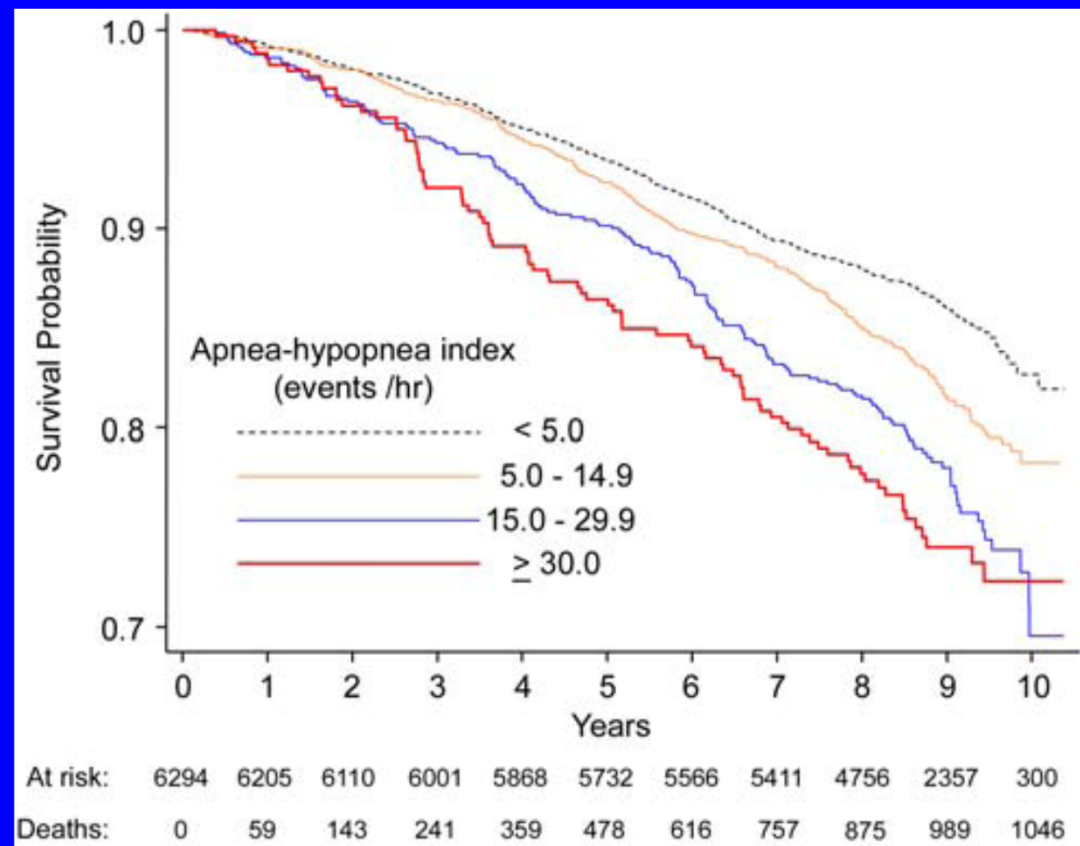
(Young et al., 1993)

30-60% in obese individuals

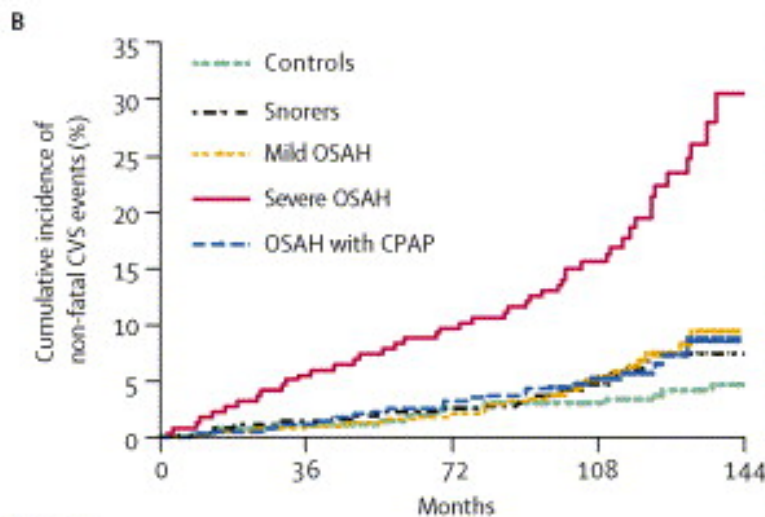
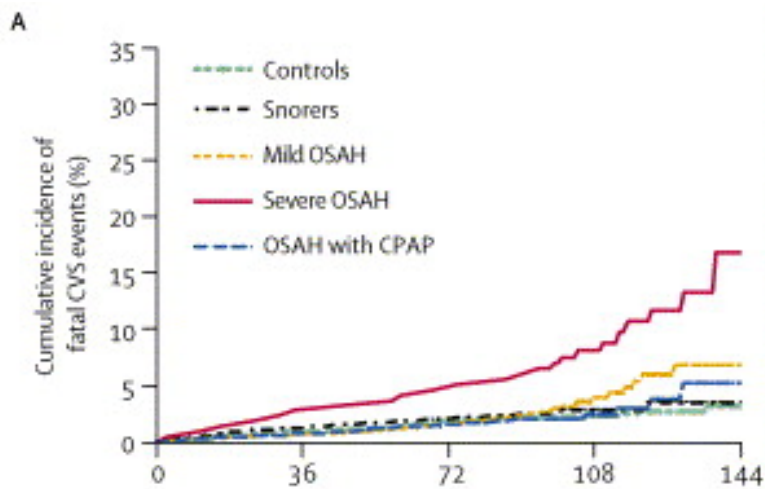
**(Vgontzas, 2000; Punjabi 2002; Young 1993 and 2002;
Tufik 2010)**



Sleep-Disordered Breathing and Mortality: a Prospective Cohort Study



Punjabi NM et al. PLoS Med. 2009 Aug;6(8):e1000132. Epub 2009 Aug 18.



Numbers at risk

Controls	264	262	259	258
Snorers	377	372	361	232
Mild OSAH	403	401	392	264
Severe OSAH	235	229	221	167
OSAH with CPAP	372	364	361	229

**Marin JM, Carrizo SJ, Vicente E, Agusti AG.
 Lancet. 2005 Mar 19-25;365(9464):1046-53.**

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

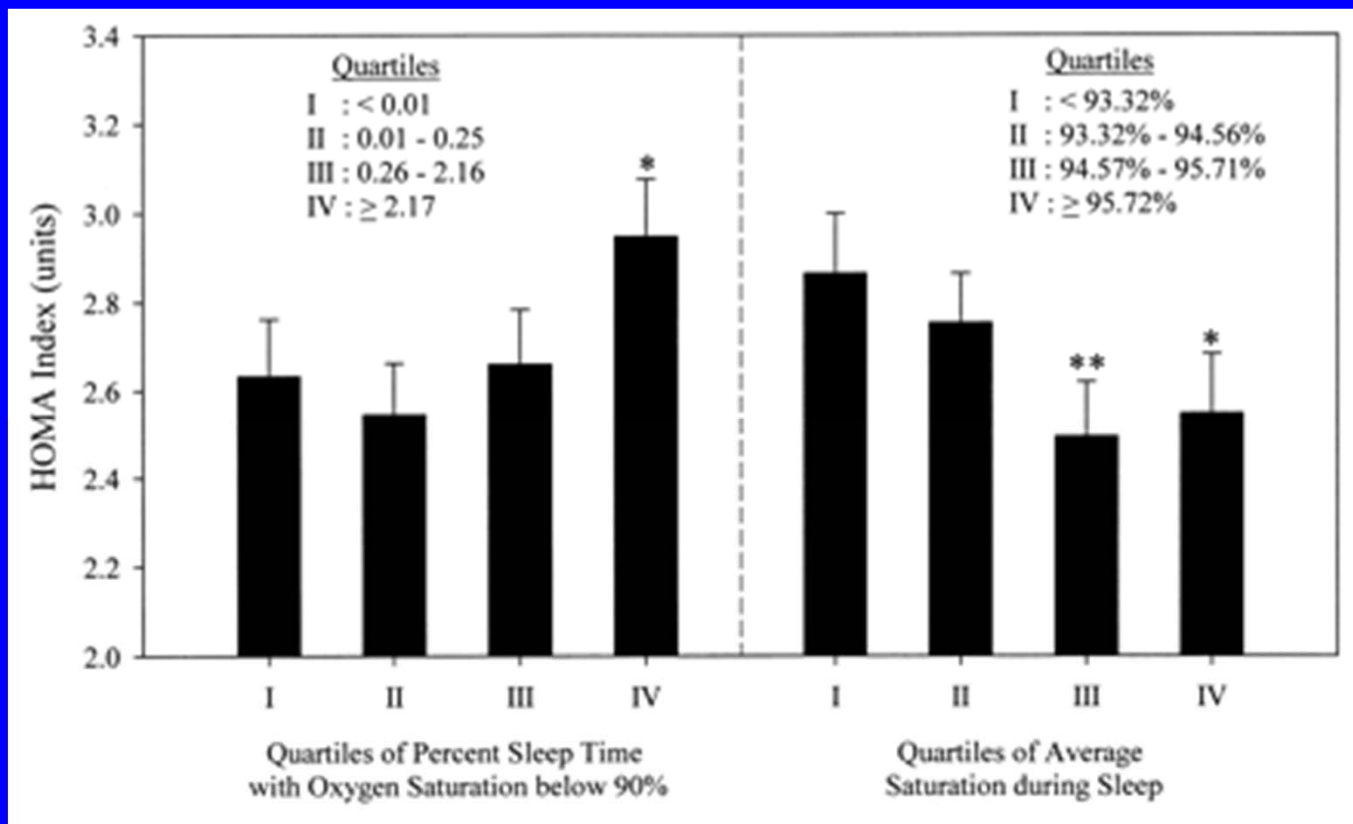
MARY S. M. IP, BING LAM, MATTHEW M. T. NG, WAH KIT LAM, KENNETH W. T. TSANG, and KAREN S. L. LAM

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

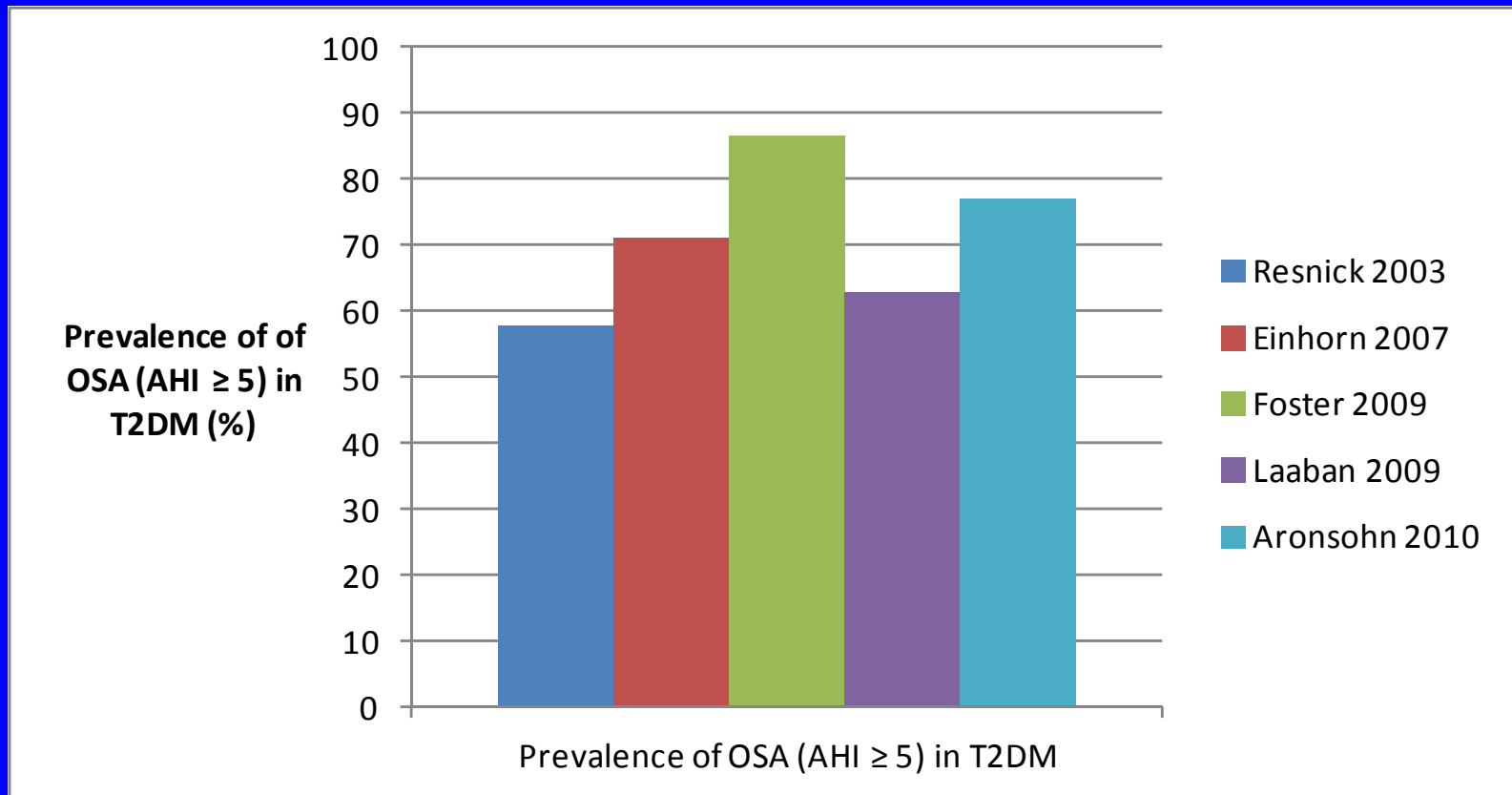


$$\text{HOMA} = G_0 \times I_0 / 22.5$$

Punjabi et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol. 2004 Sep 15;160(6):521-30.

Prevalence of OSA in T2DM

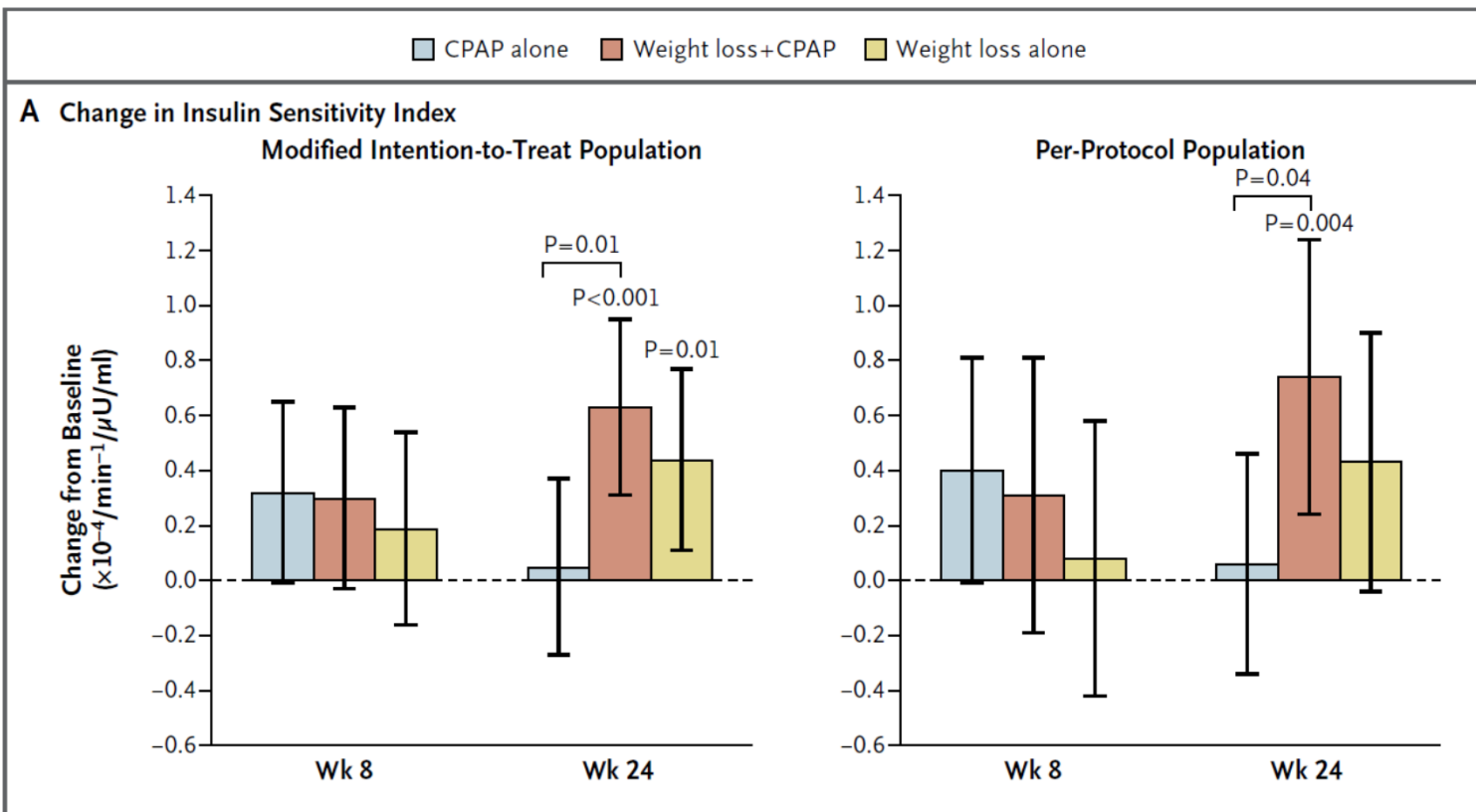
(adapted from Pamidi and Tasali,
Front Neurol. 2012;3:126. Epub 2012 Aug 13)



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.

N Engl J Med 2014;370:2265-75.

CPAP effect

New data from Punjabi and Tasali presented at ATS 2014 indicate significant improvement of insulin resistance with CPAP

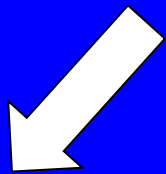
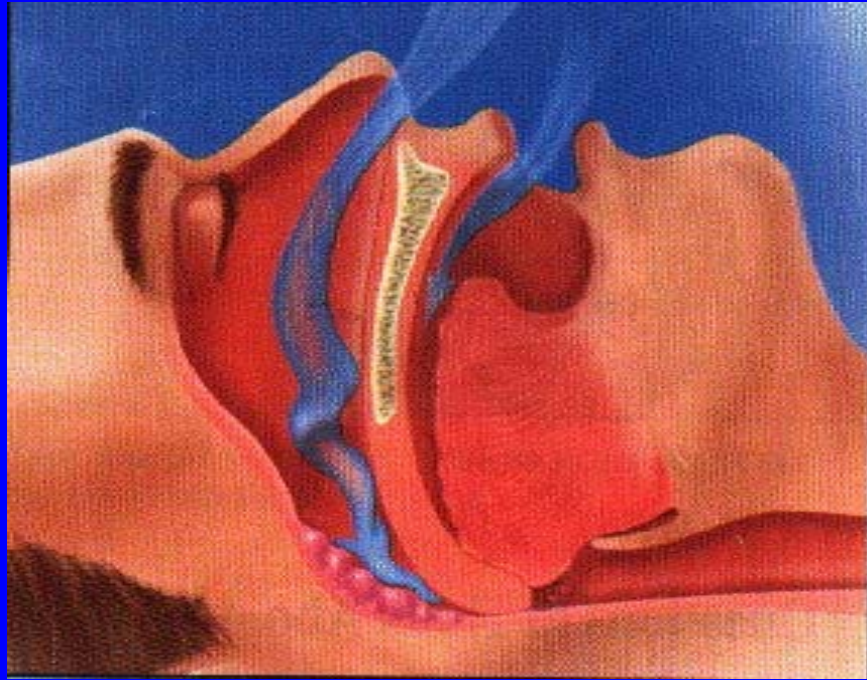
What are the mechanisms ?



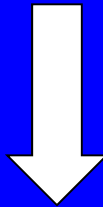
i has a cheezie



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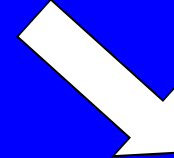
**Intermittent
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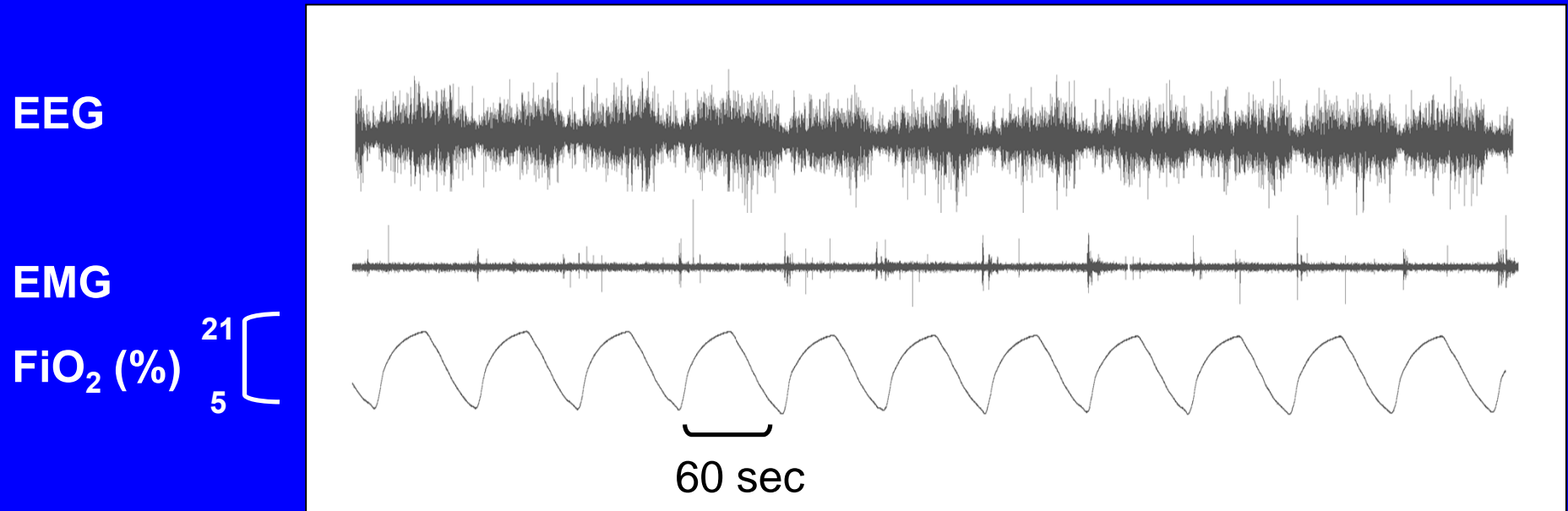
Hypercapnea

Mouse Model of Intermittent Hypoxia



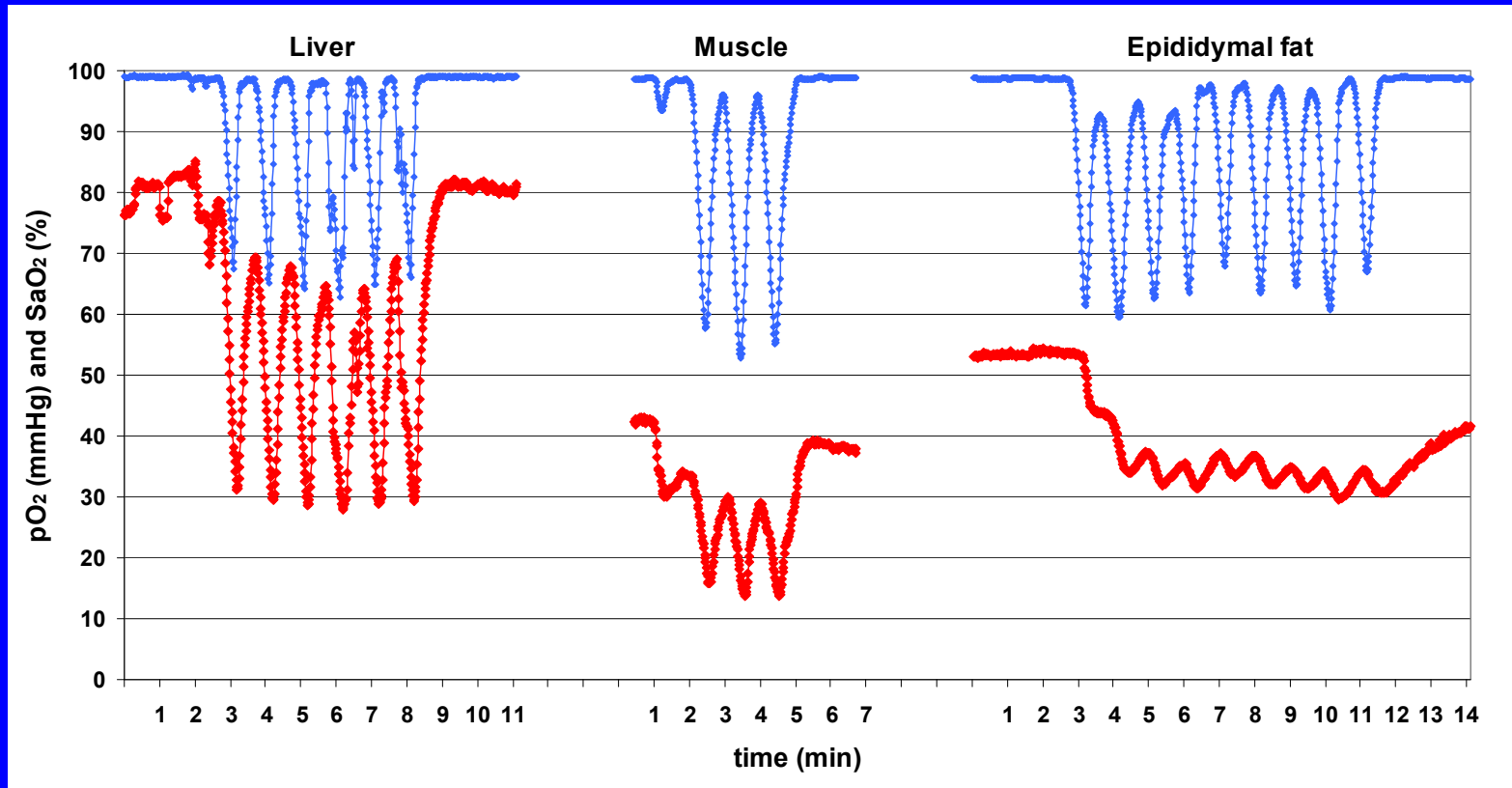


Intermittent Hypoxia is a Complex Stimulus: IH Events Fragment Sleep



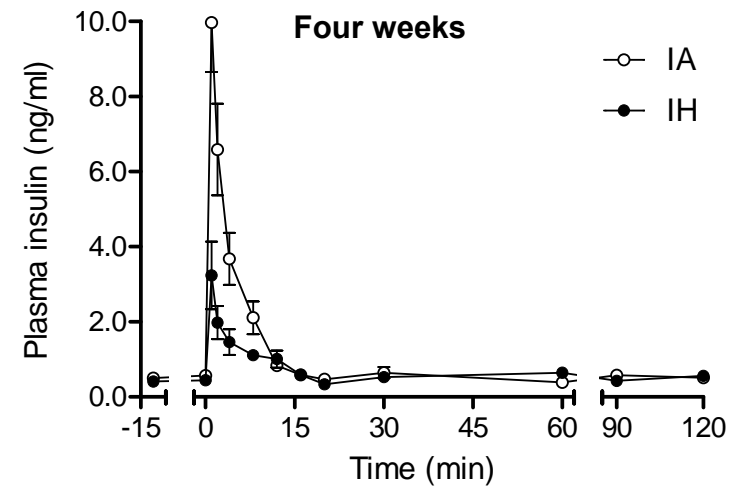
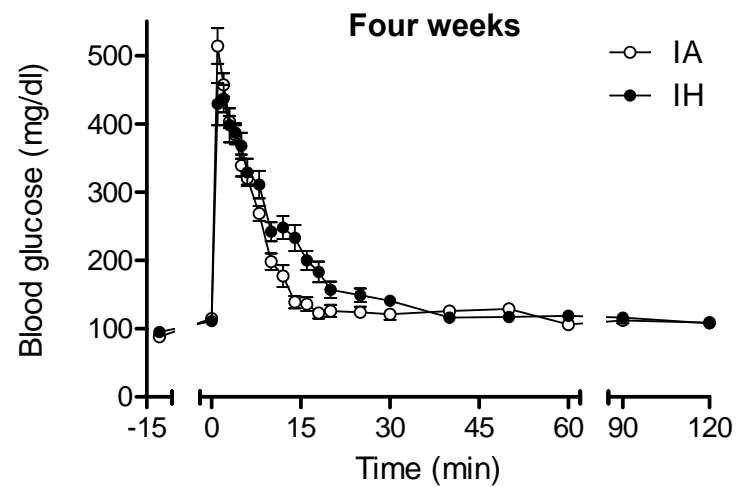
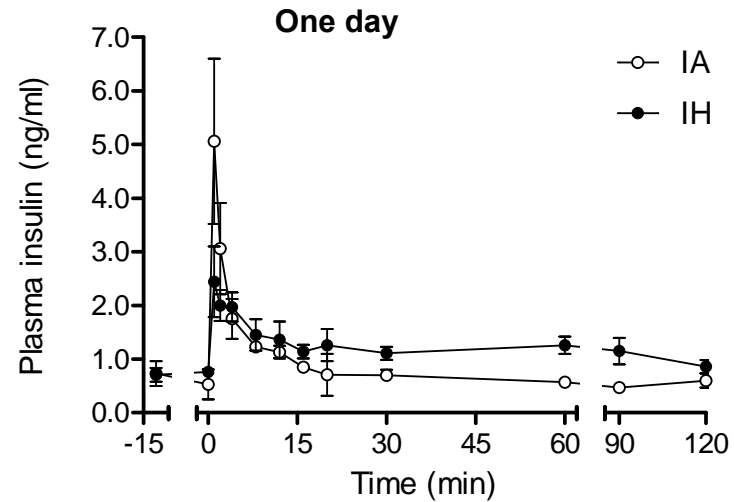
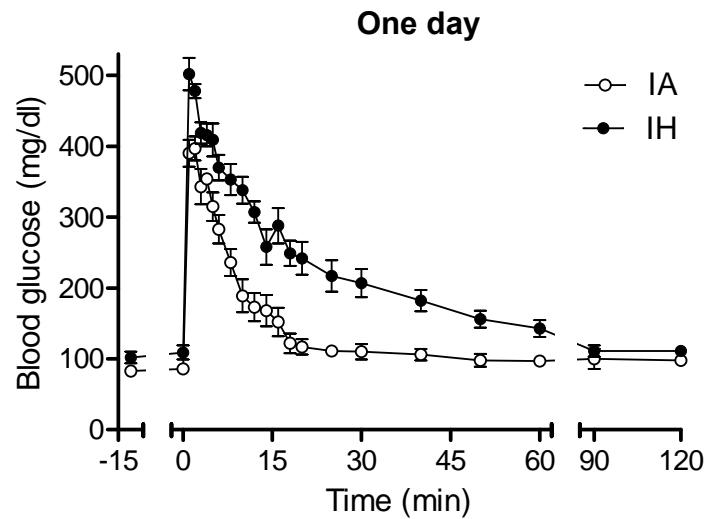
Polotsky et al. Sleep Med. 2006 Jan;7(1):7-16.

Mouse Model of Intermittent Hypoxia



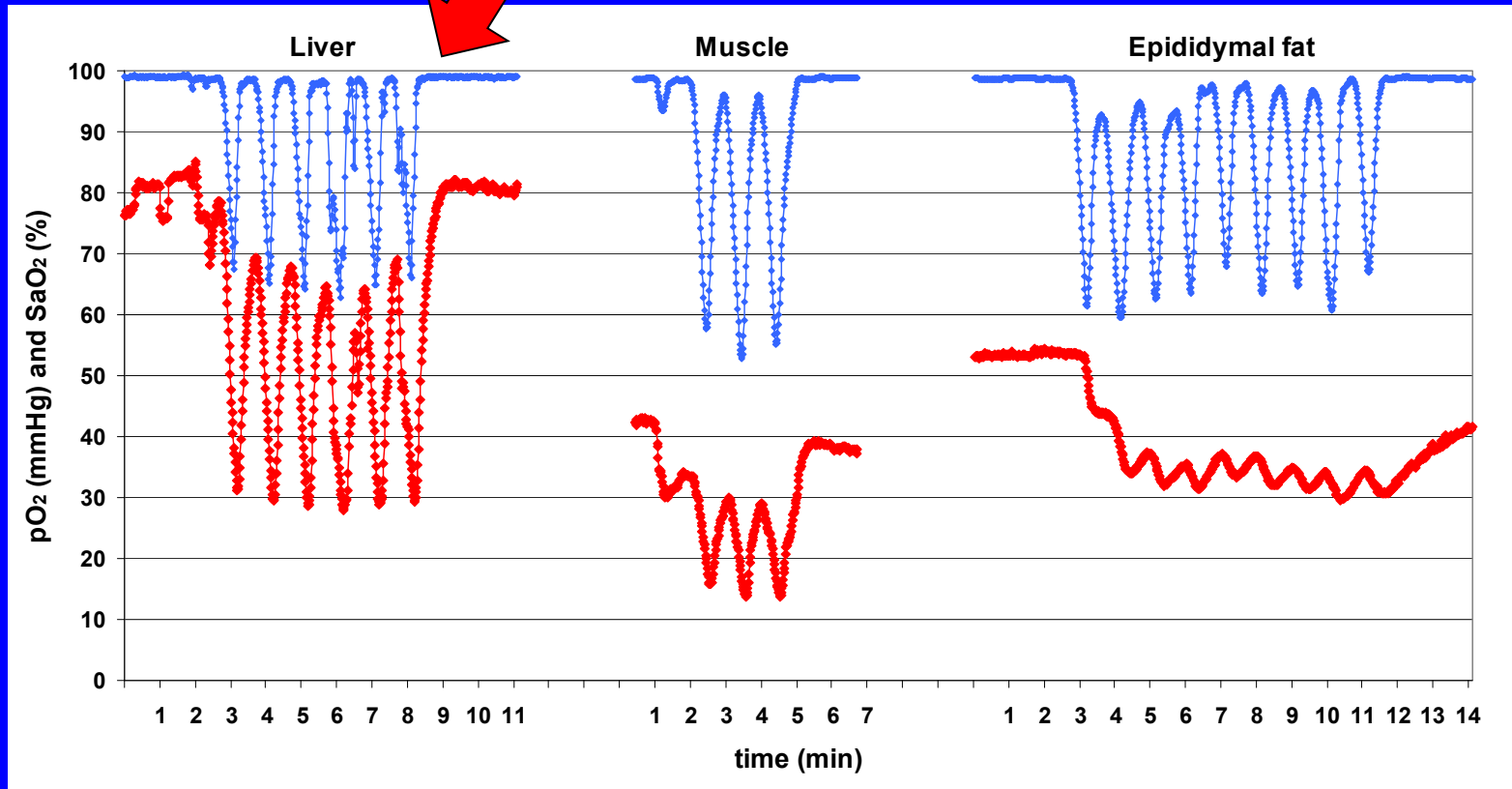
Reinke et al. J Appl Physiol 2011, 111:881-90

Intermittent Hypoxia Increases Insulin Resistance and Suppresses Insulin Secretion



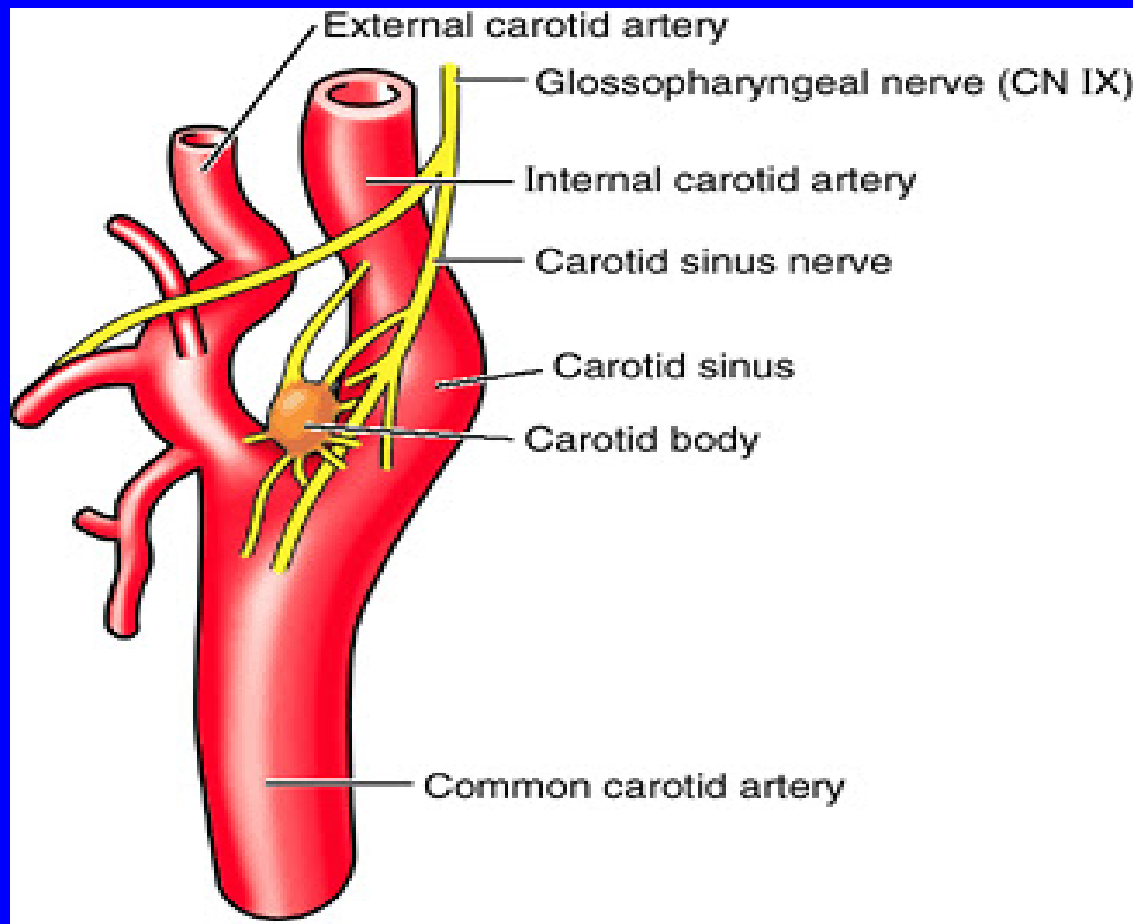
Mouse Model of Intermittent Hypoxia

Systemic Effects (Carotid bodies, SNS)

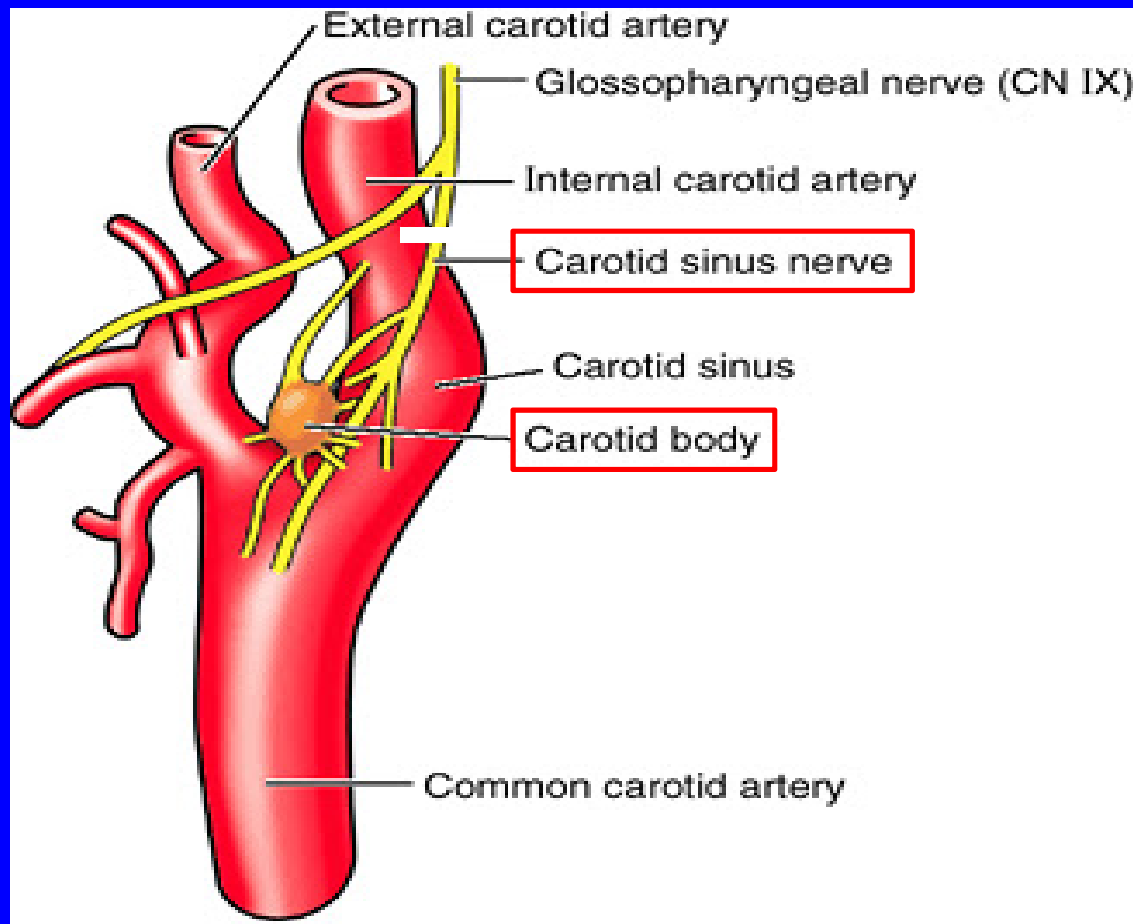


Reinke et al. J Appl Physiol 2011, 111:881-90

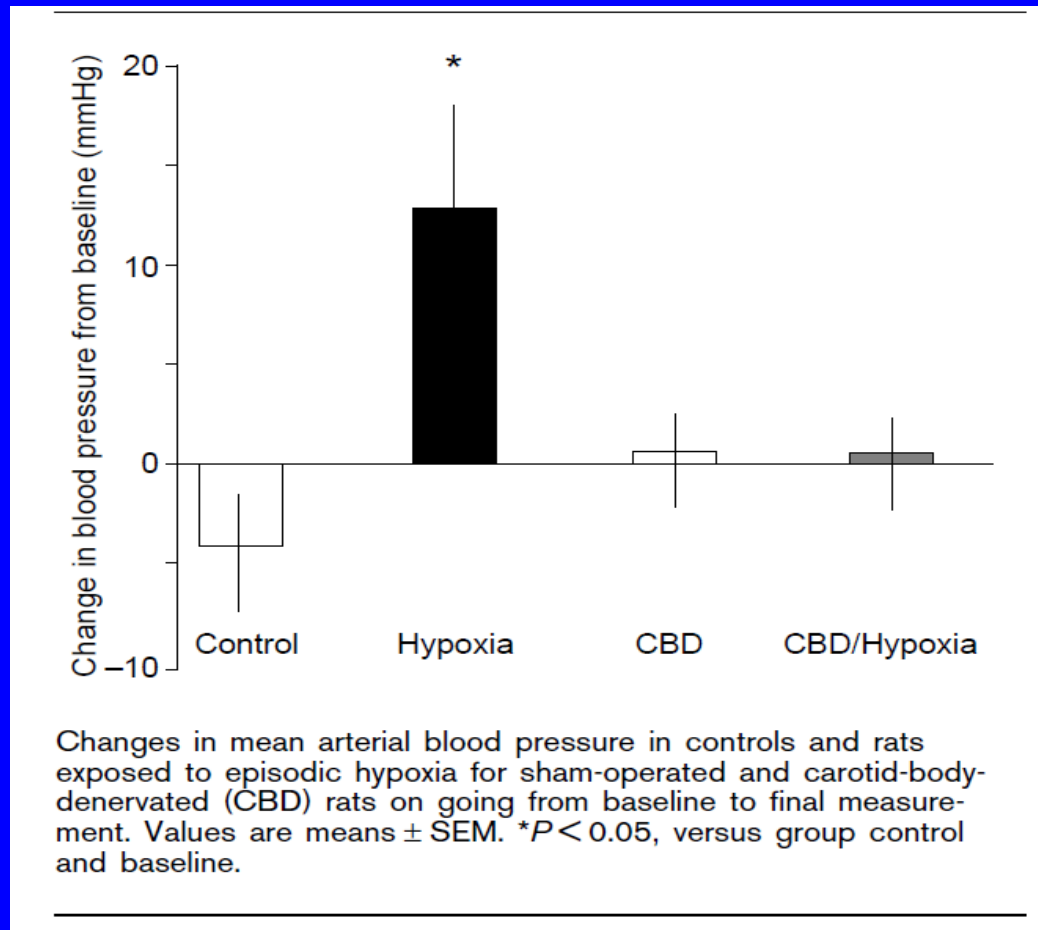
Carotid Body governs systemic responses to Intermittent Hypoxia



Carotid Sinus Nerve Dissection

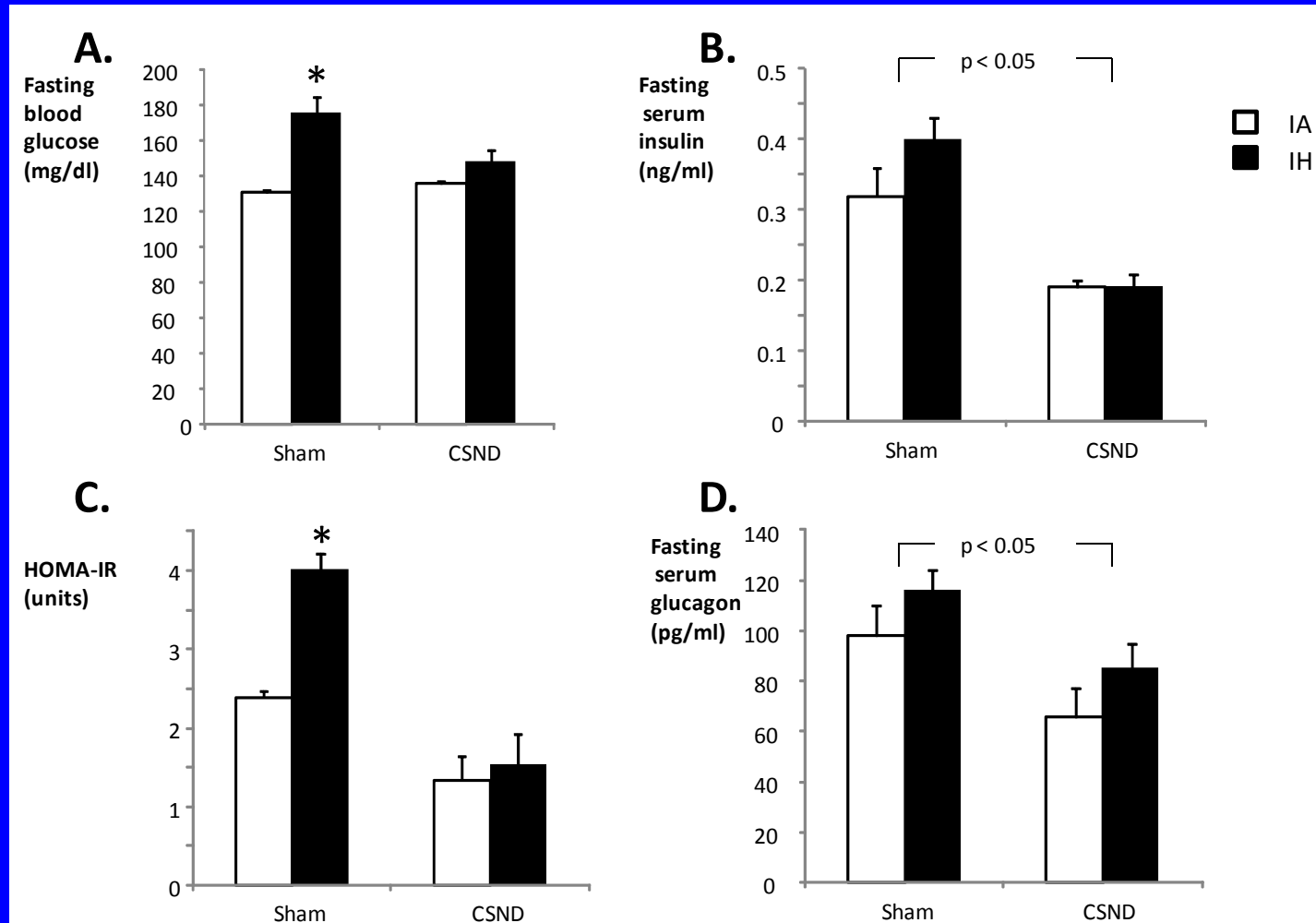


Carotid Body governs systemic responses to Intermittent Hypoxia



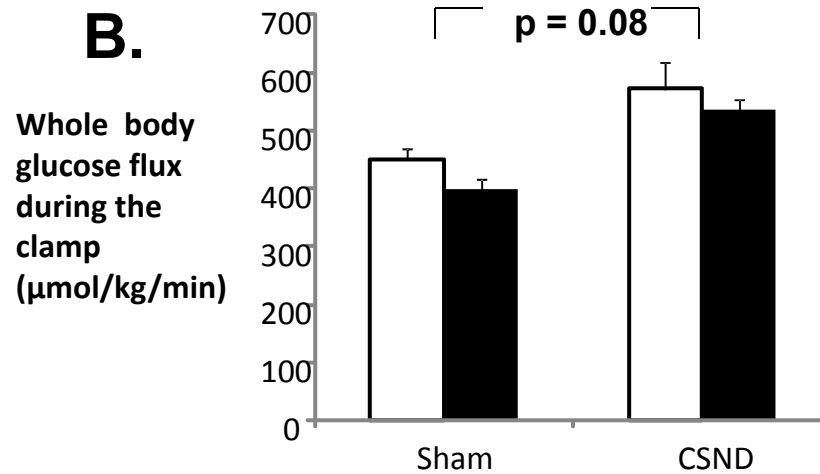
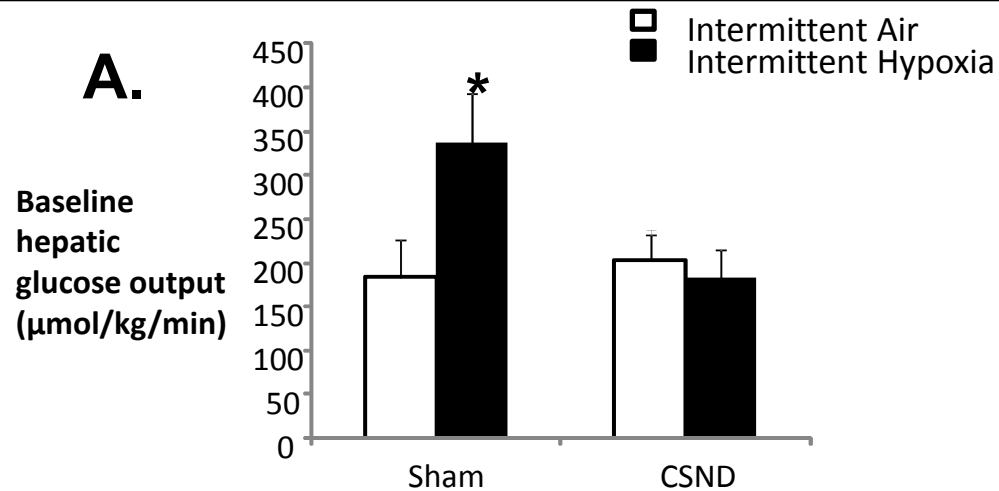
Lesske et al. Journal of Hypertension. 1997. 15:1593-1603.

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

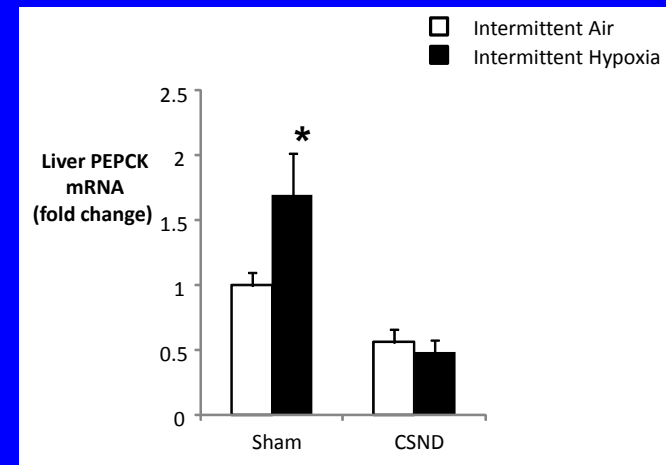
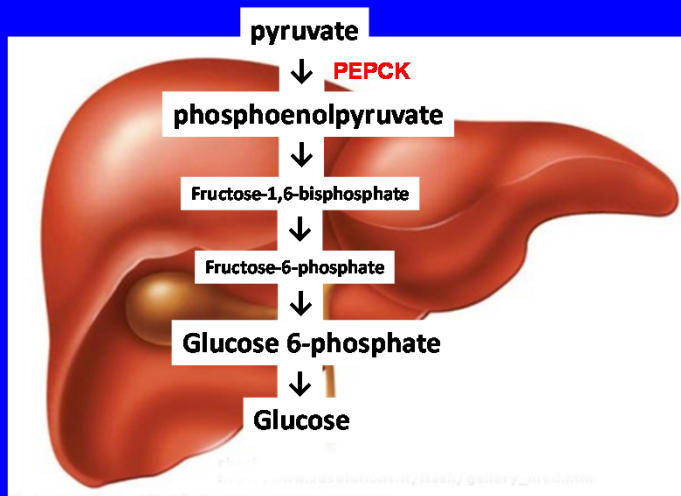


Shin et al. J Appl Physiol. 2014 Oct 1;117(7):765-76.

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

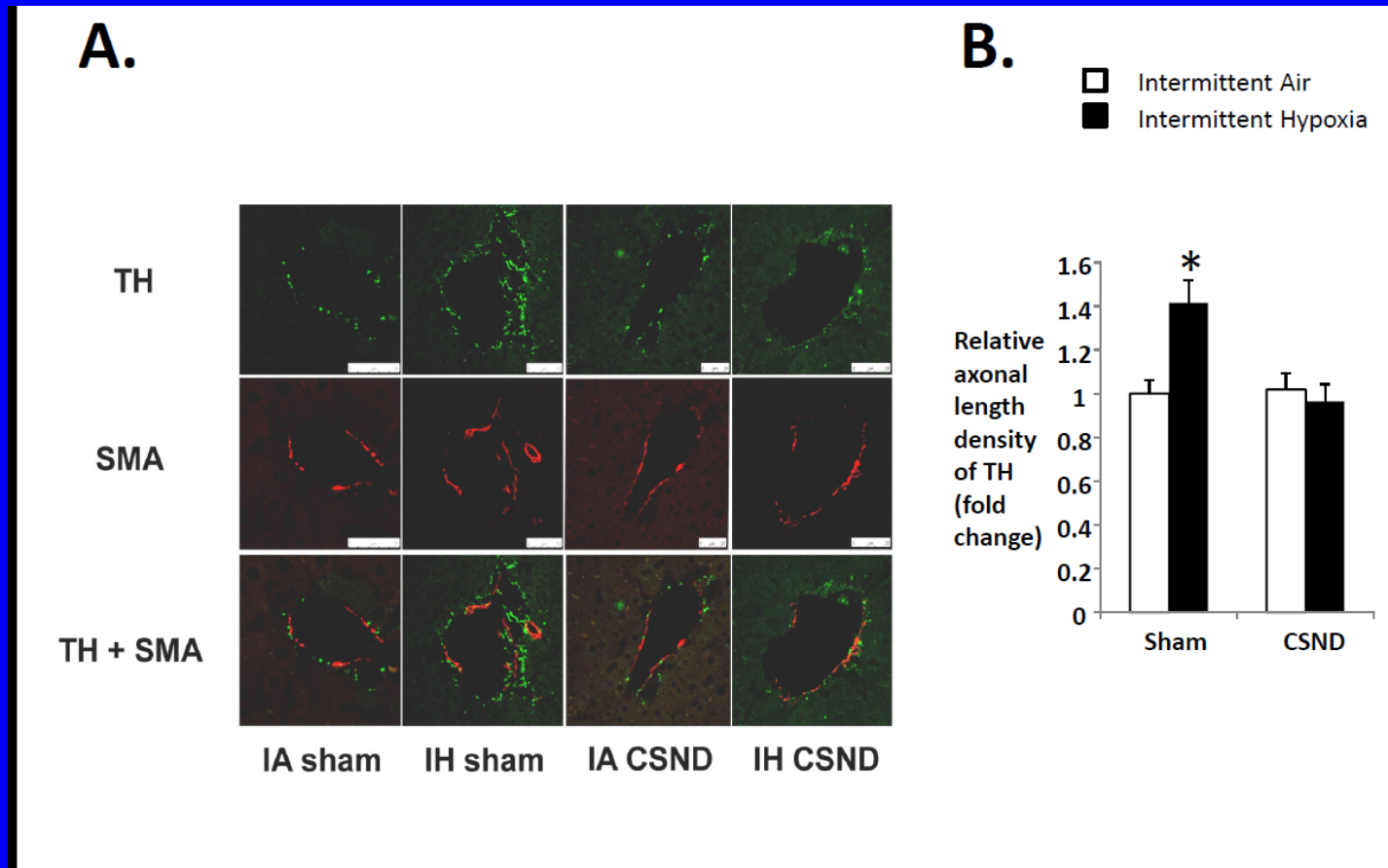


Carotid Sinus Nerve Dissection (CSND) prevents an IH-induced increase in gluconeogenesis



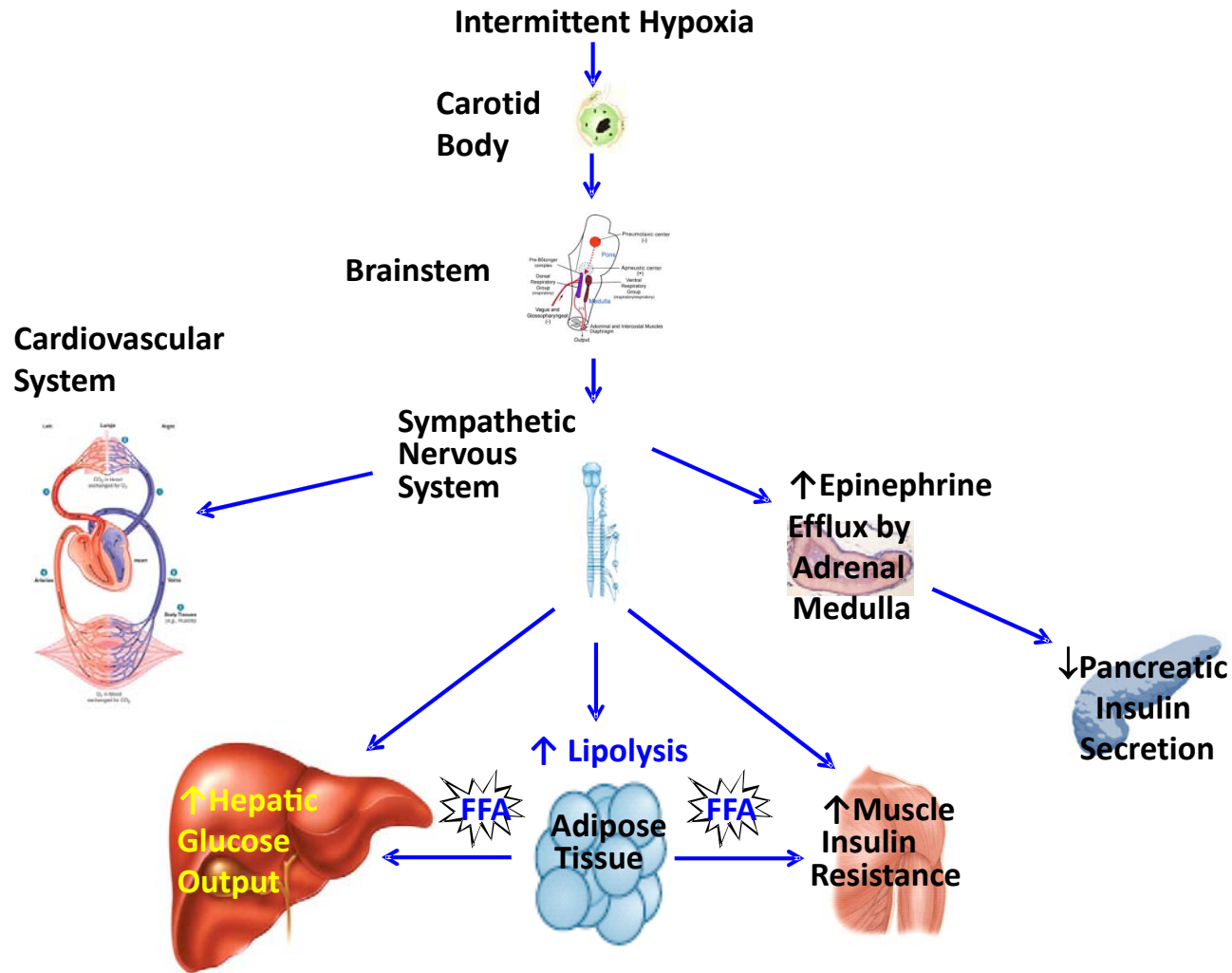
Shin et al. J Appl Physiol. 2014 Oct 1;117(7):765-76.

CSND abolishes sympathetic activation in the liver



Shin et al. J Appl Physiol. 2014 Oct 1;117(7):765-76.

Carotid Body Governs Systemic Responses to Intermittent Hypoxia



- **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				Overall	p value	
	0-<1.25	1.25-<4.0	4.0-<10.7	≥10.7-115.6		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 (39.3)	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	135.6 (130.4)	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

Relation of Sleep-disordered Breathing to Cardiovascular Disease Risk Factors: The Sleep Heart Health Study. Newman et al. Am J Epidemiol 2001;154:50-9.

CPAP and Plasma Lipids: Randomized Studies

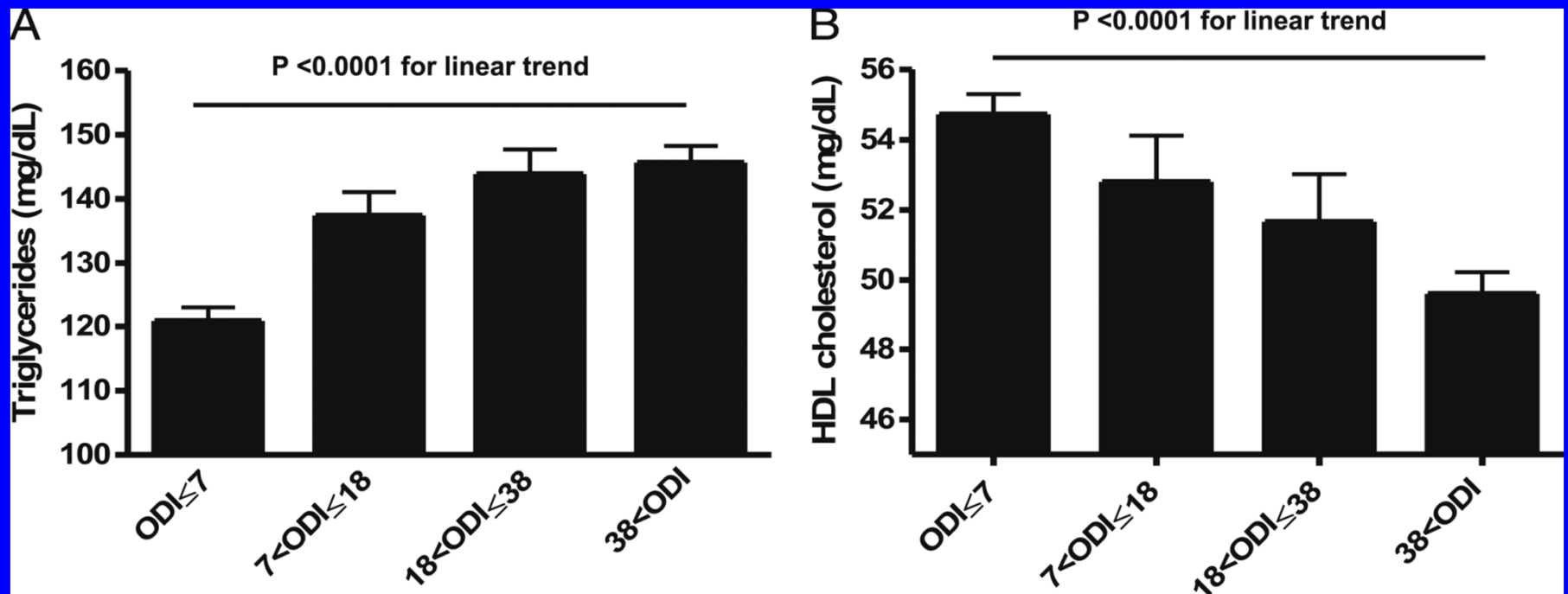
	Therapeutic CPAP		Subtherapeutic CPAP	
	Day 0 (SD)	Day 30 change (CI)	Day 0 (SD)	Day 30 change (CI)
Total cholesterol				
mg/dl	220 (43)	-10.8 (-17.4 to -4.2)	216 (43)	-2.7(-2.3 to 8.1)
mmol/l	5.7 (1.1)	-0.28 (-0.45 to -0.11)	5.6 (1.1)	-0.07(-0.06 to 0.21)
Tryglicerides				
mg/dl	230 (168)	-21.2 (-24.8 to 67.3)	292 (221)	-4.4 (-39.8 to 32)
mmol/l	2.6 (1.9)	-0.24 (-0.28 to 0.76)	3.3 (2.5)	-0.05 (-0.45 to 0.36)

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

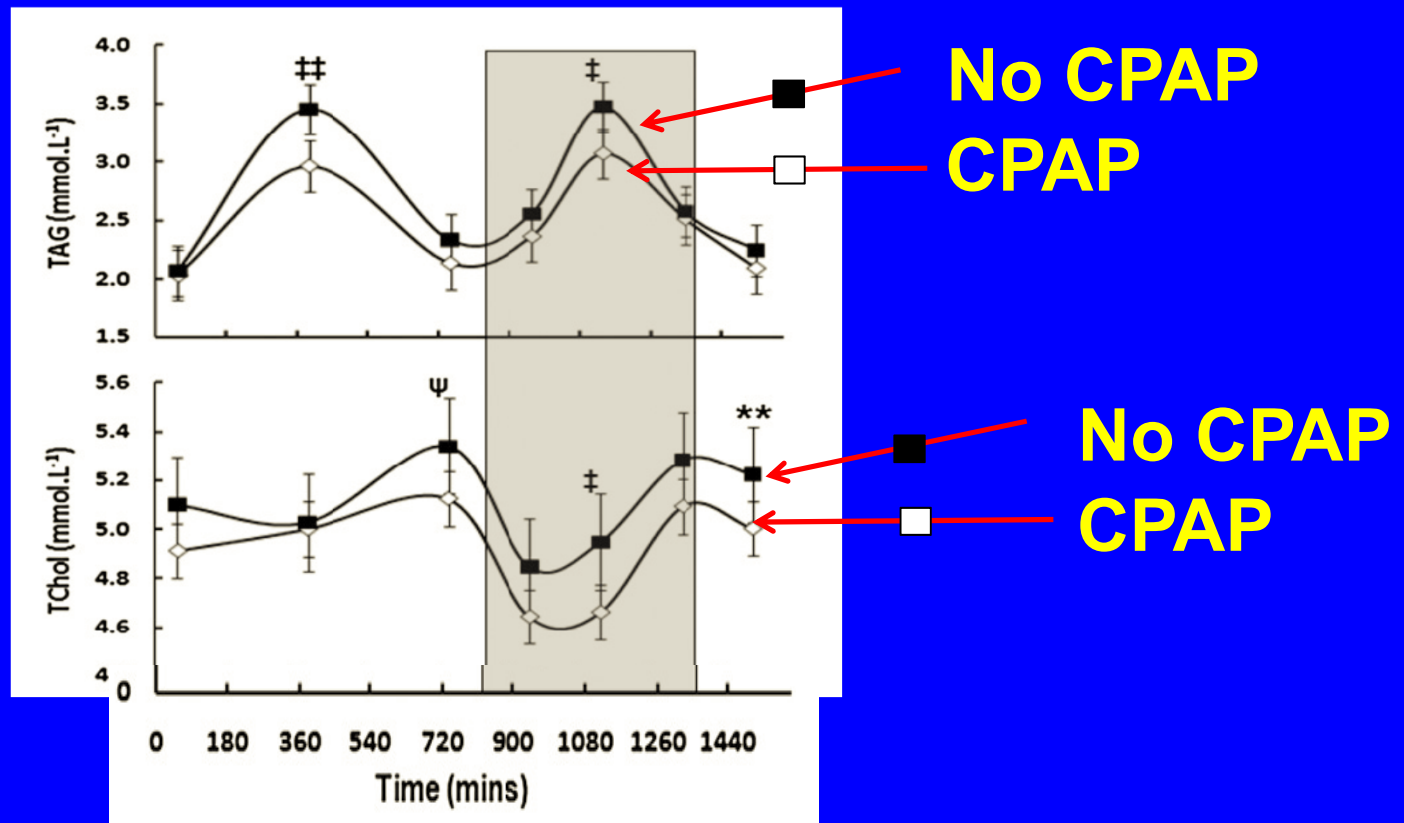
.....
Thorax 2004;59:777-782. doi: 10.1136/thx.2003.018739

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



Trzepizur et al. Chest . 2013; 143:1584-9.

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



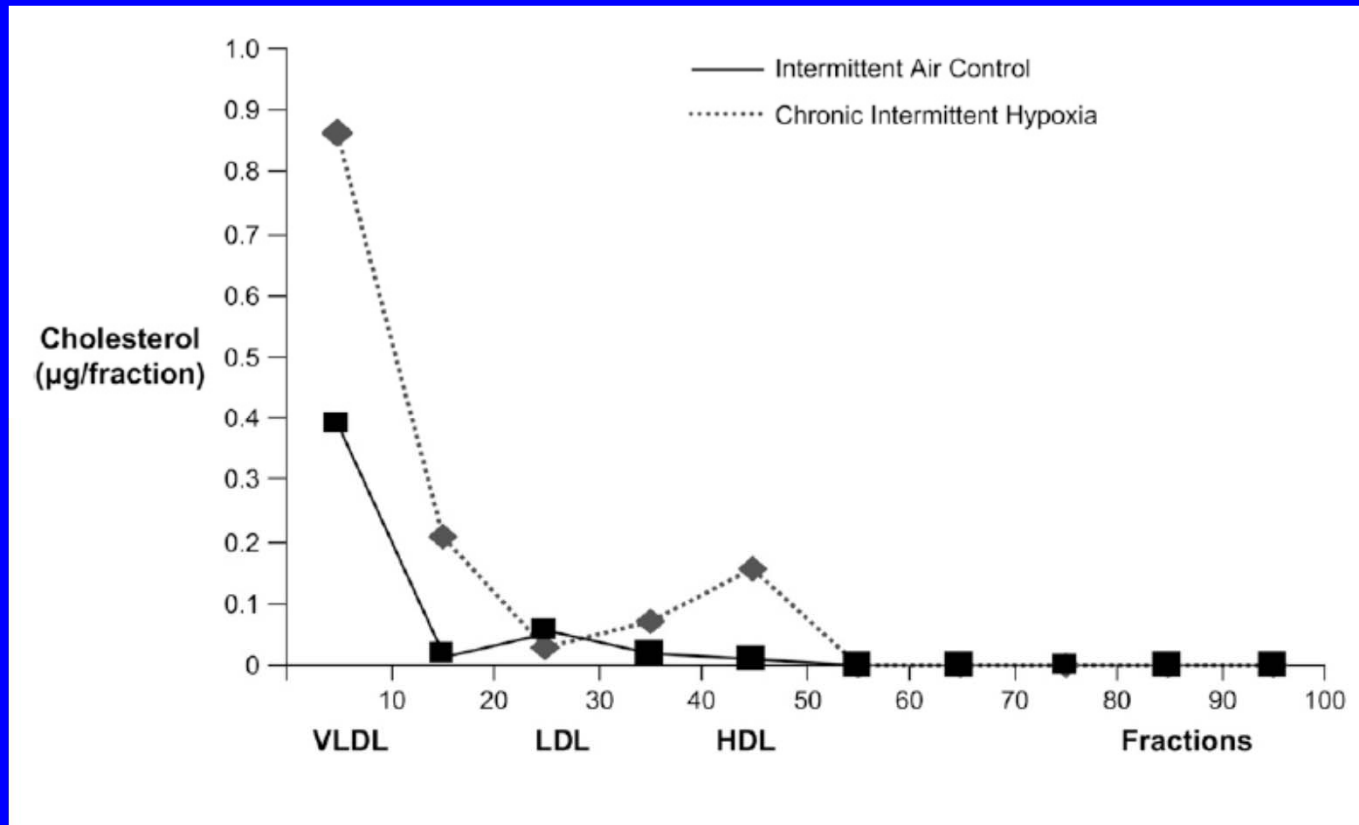
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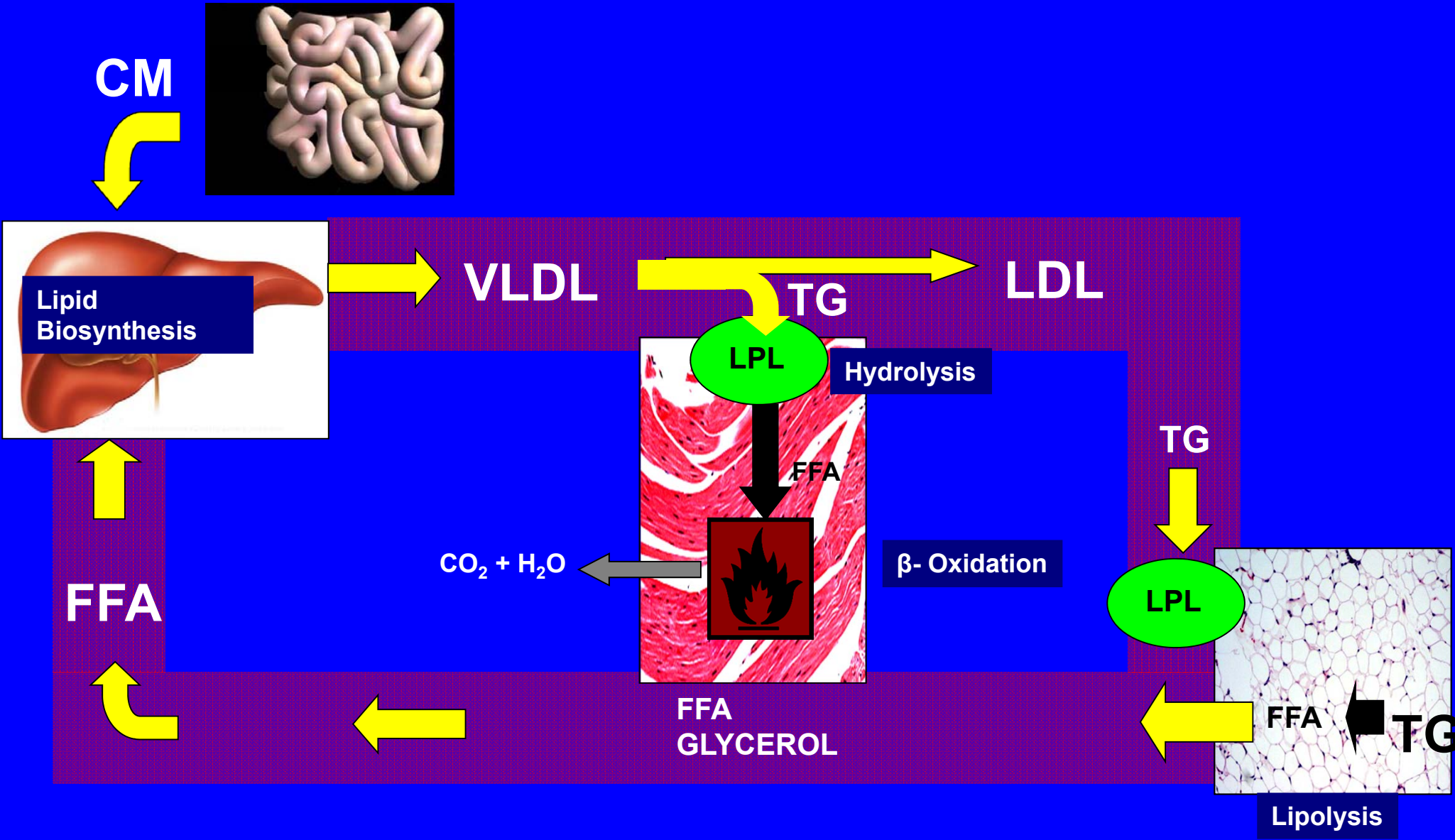
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Intermittent Hypoxia increases VLDL levels

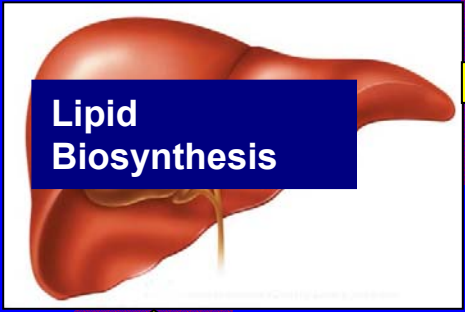
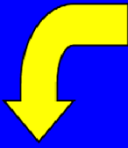
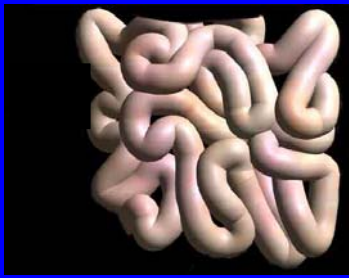
CIH for 12 weeks in C57BL/6J mice



Savransky V, Nanayakkara A, Li J, Bevans S, Smith PL, Rodriguez A, Polotsky VY. 2007. Am J Resp Crit Care Med. 175: 1290-7



CM



VLDL

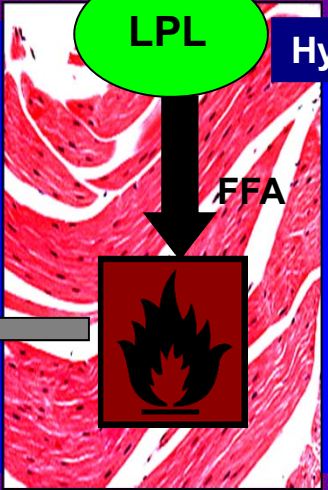


LDL

TG



Hydrolysis



FFA



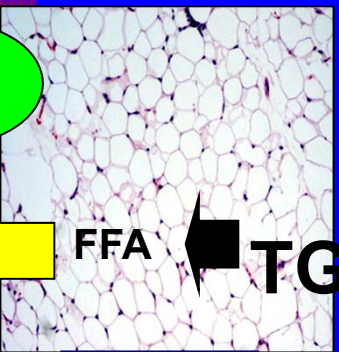
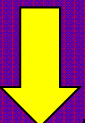
β- Oxidation

CO₂ + H₂O



FFA
GLYCEROL

TG

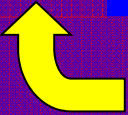


FFA

TG

Lipolysis

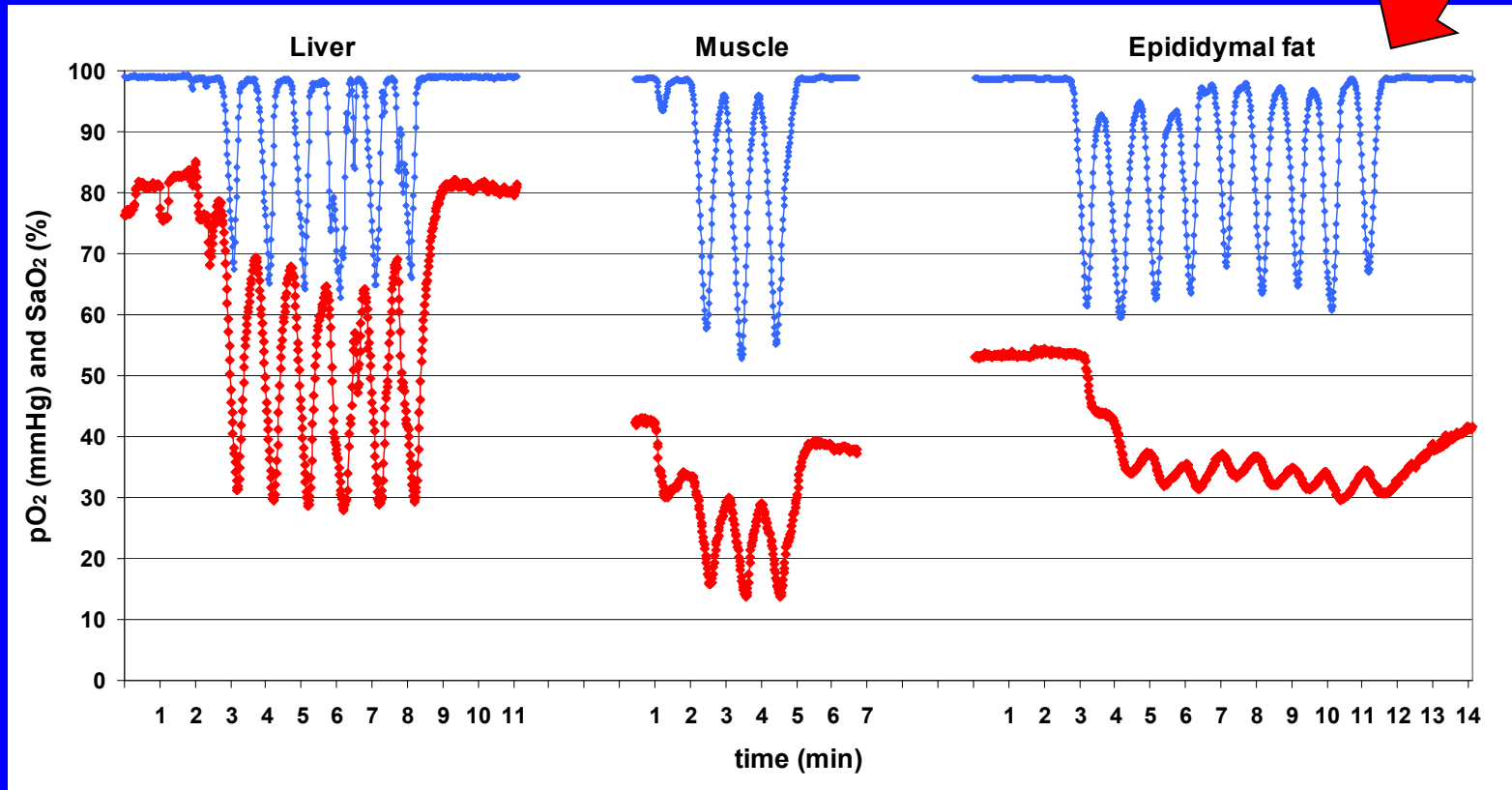
FFA



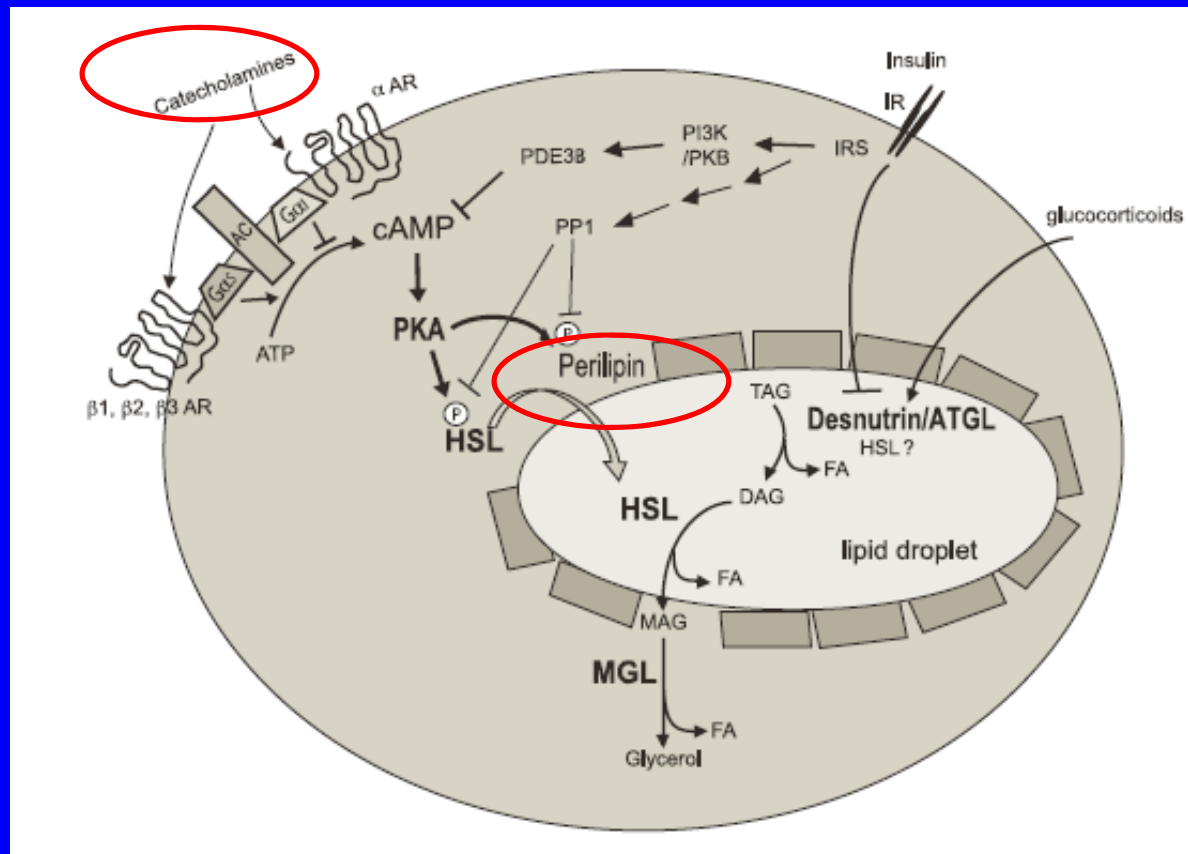
Intermittent Hypoxia and Adipose Tissue Lipolysis

Mouse Model of Intermittent Hypoxia

Systemic Effects (Carotid bodies, SNS)



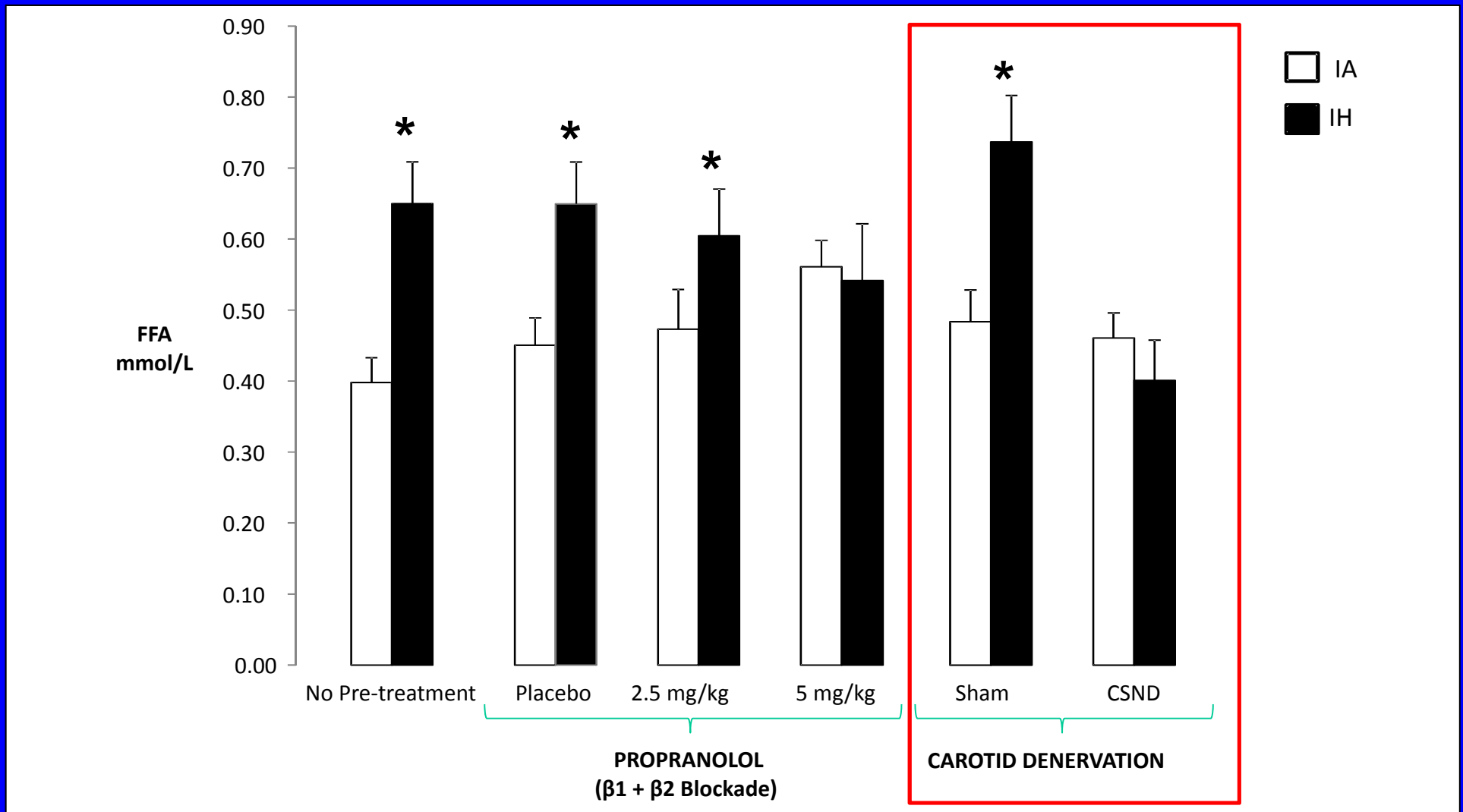
Lipolysis in Adipose Tissue



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

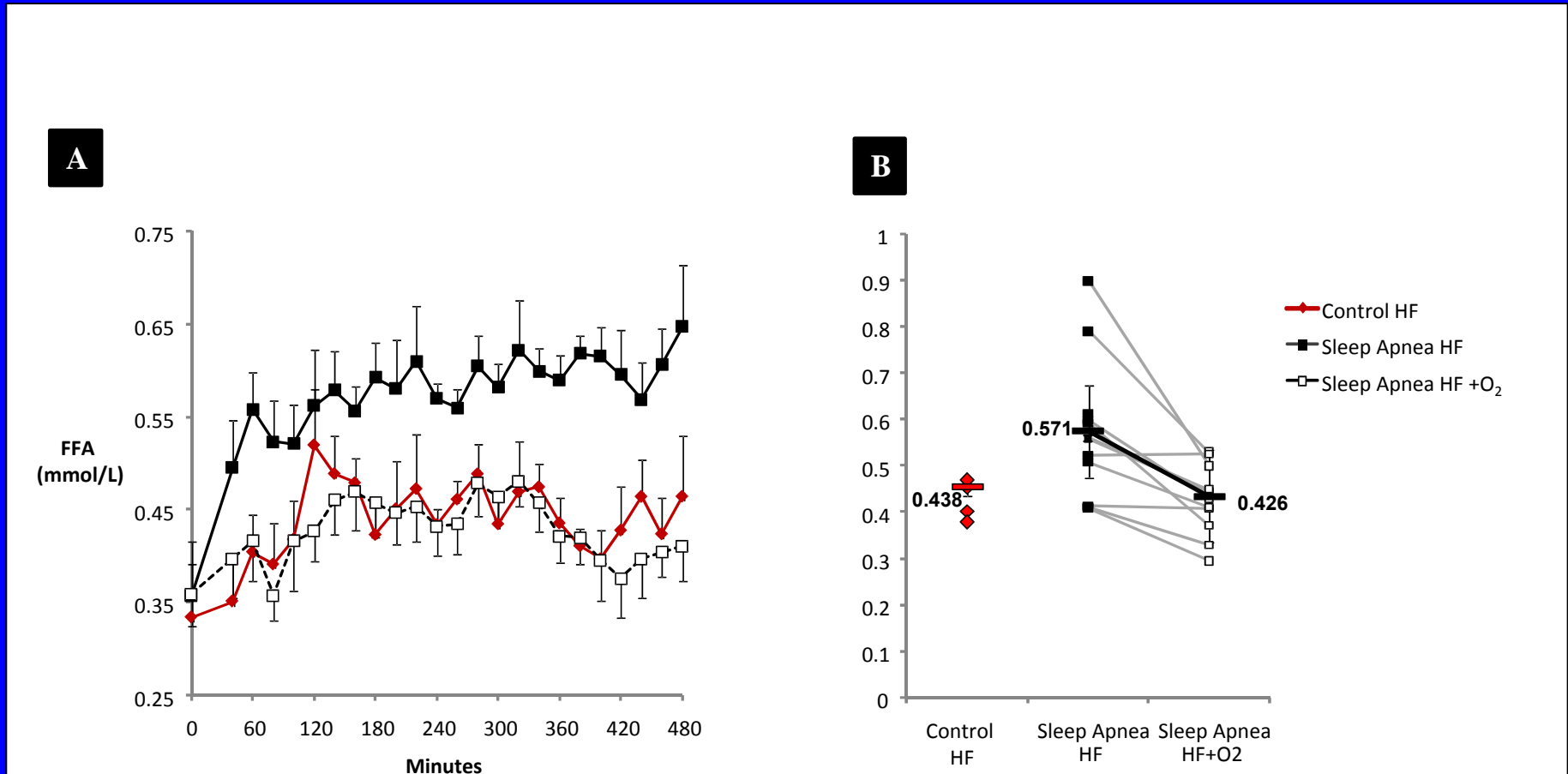
Am J Physiol Gastrointest Liver Physiol 293:1-4, 2007. First published Jan 11, 2007;
doi:10.1152/ajpgi.00554.2006

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



Jun et al. Am J Physiol Endocrinol Metab. 2014 Oct. [Epub ahead of print]

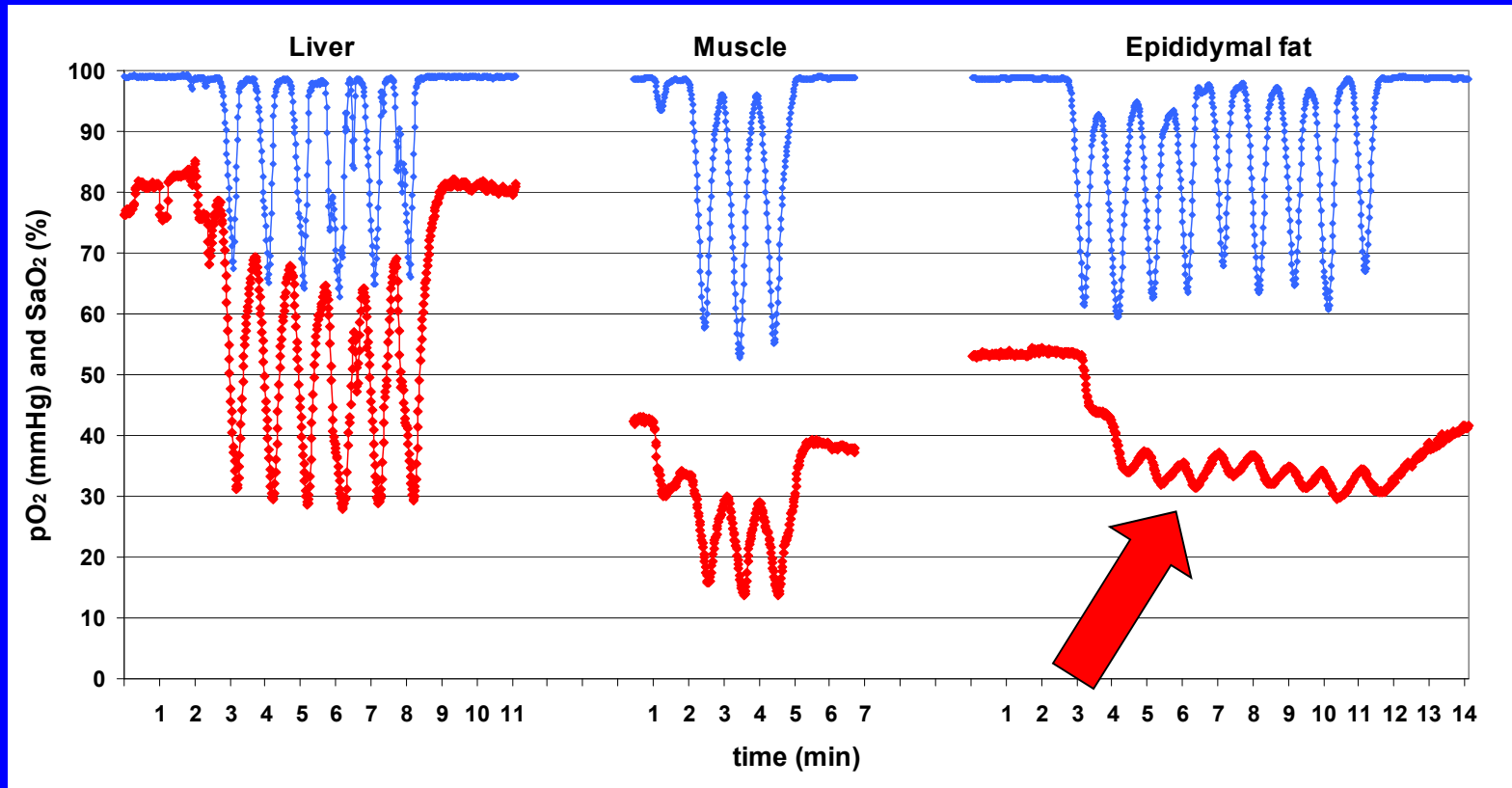
In patients with sleep apnea nocturnal elevation of plasma FFA levels is caused by IH



Jun et al. Sleep. 2011; 33:783-90.

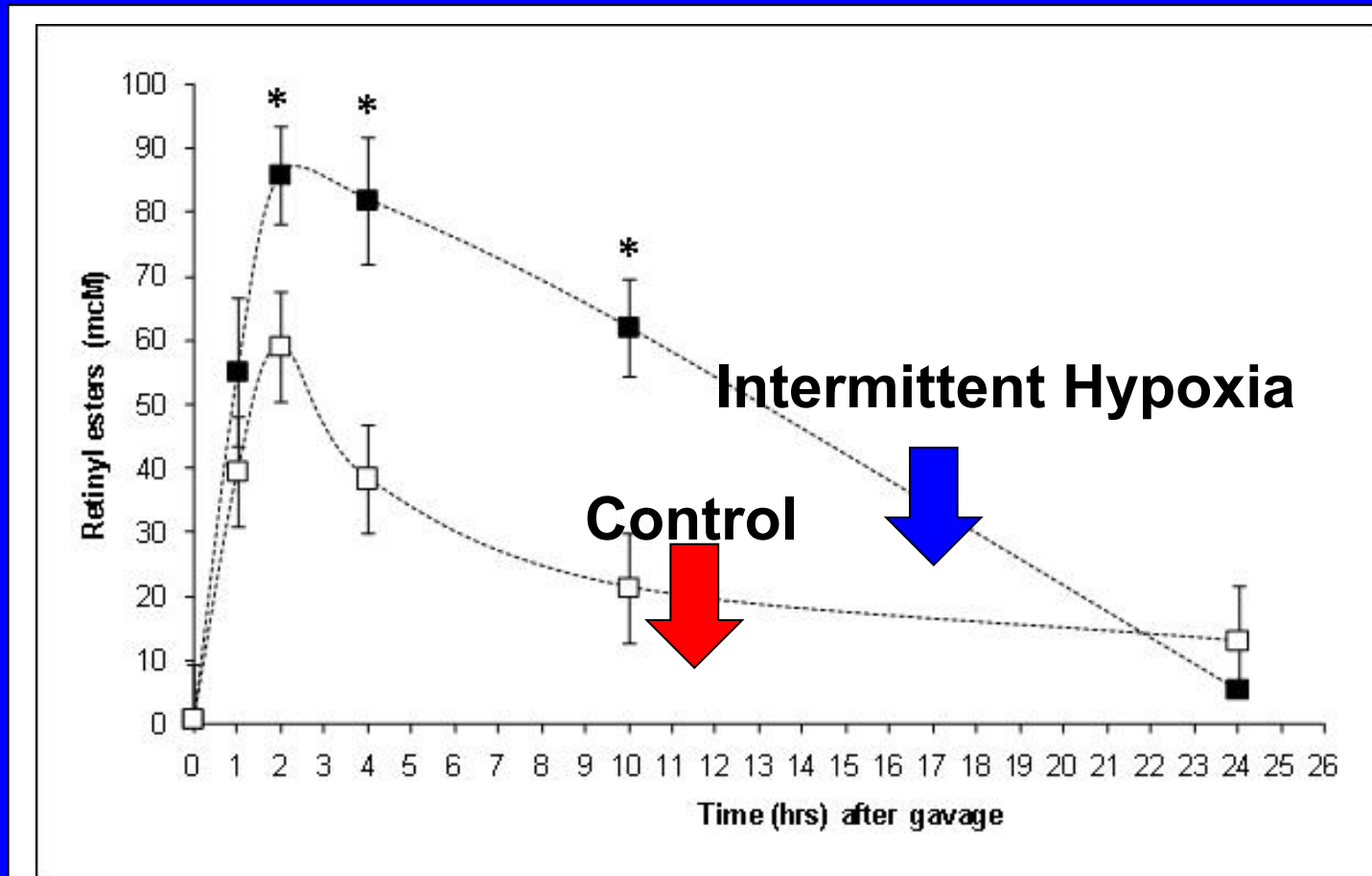
Intermittent Hypoxia and Lipoprotein Clearance

Mouse Model of Intermittent Hypoxia



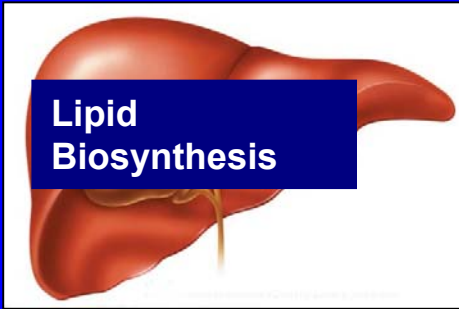
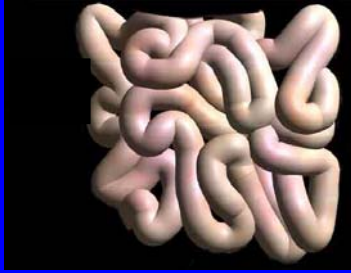
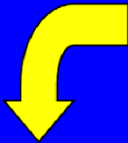
Tissue Specific Effects (Hypoxia inducible factors, etc)

Intermittent Hypoxia Decreases Chylomicron Clearance



Drager et al. Eur Heart J . 2012; 33:783-90.

CM



VLDL



LDL

TG



Hydrolysis

FFA

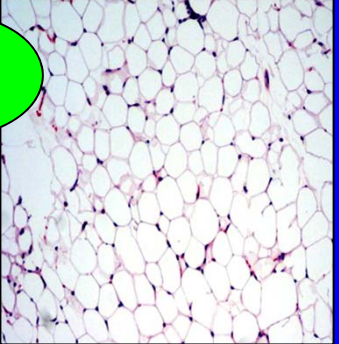
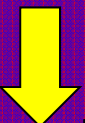


β - Oxidation

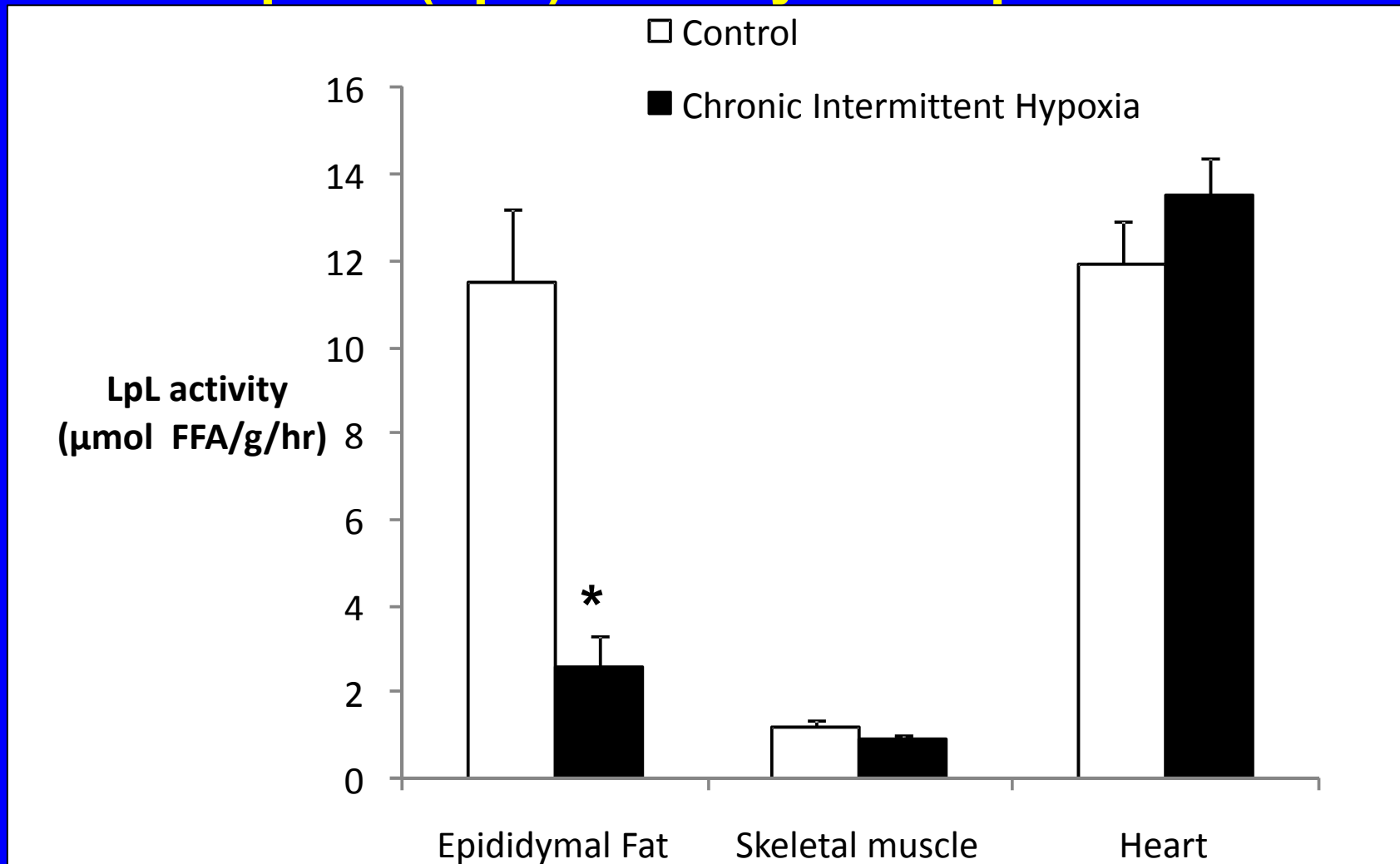
$\text{CO}_2 + \text{H}_2\text{O}$



TG

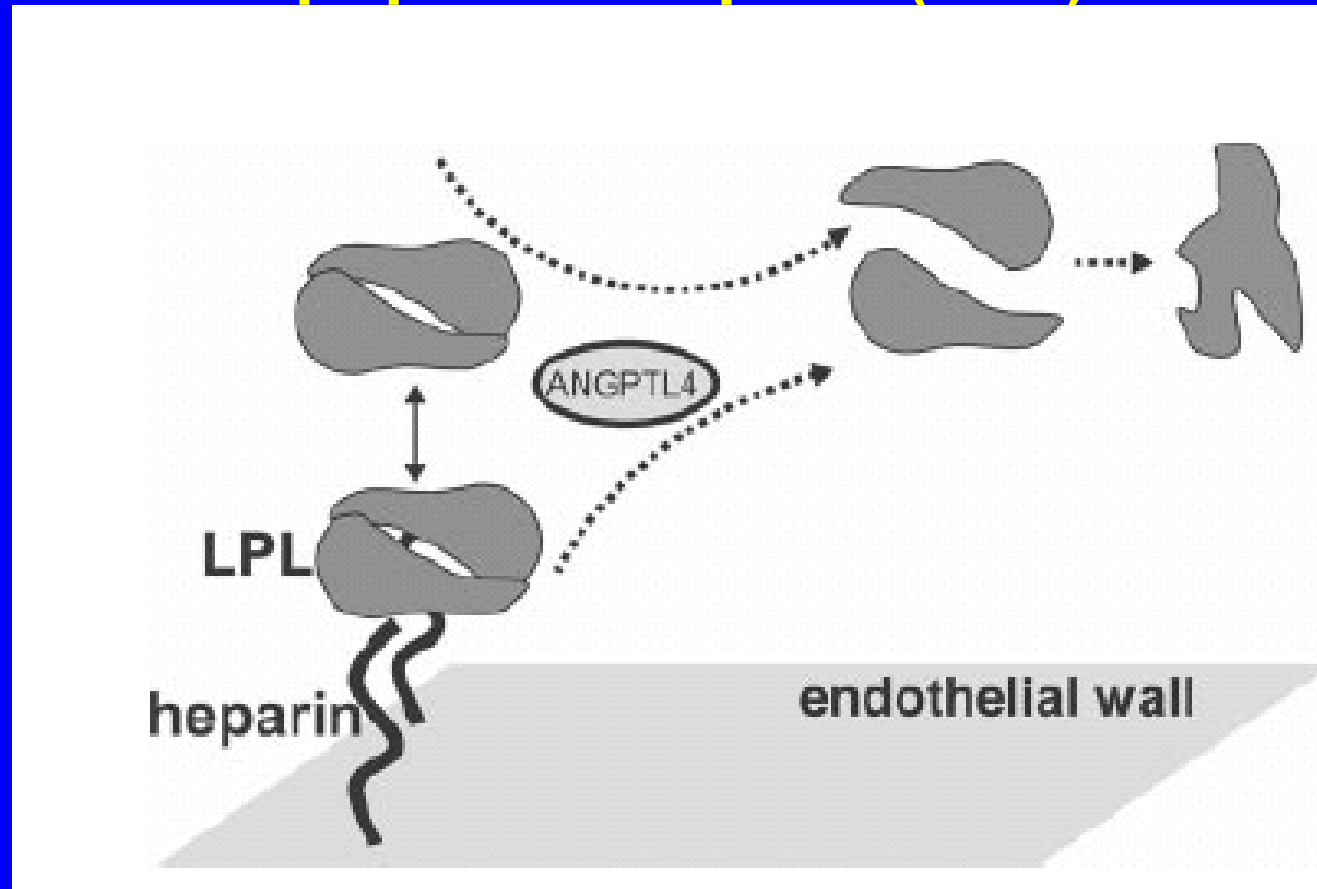


Intermittent Hypoxia Decreases Lipoprotein Lipase (LpL) Activity in Adipose Tissue



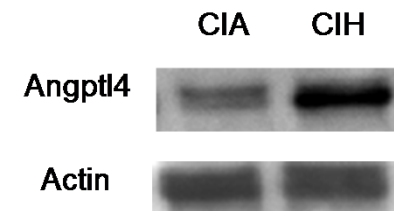
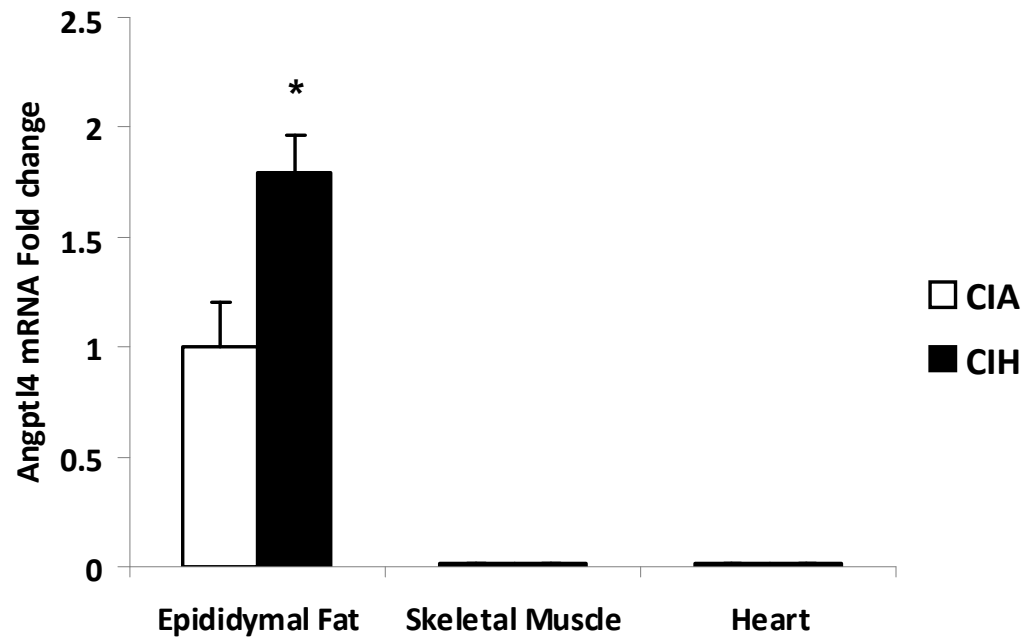
Drager et al. Eur Heart J . 2012; 33:783-90.

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



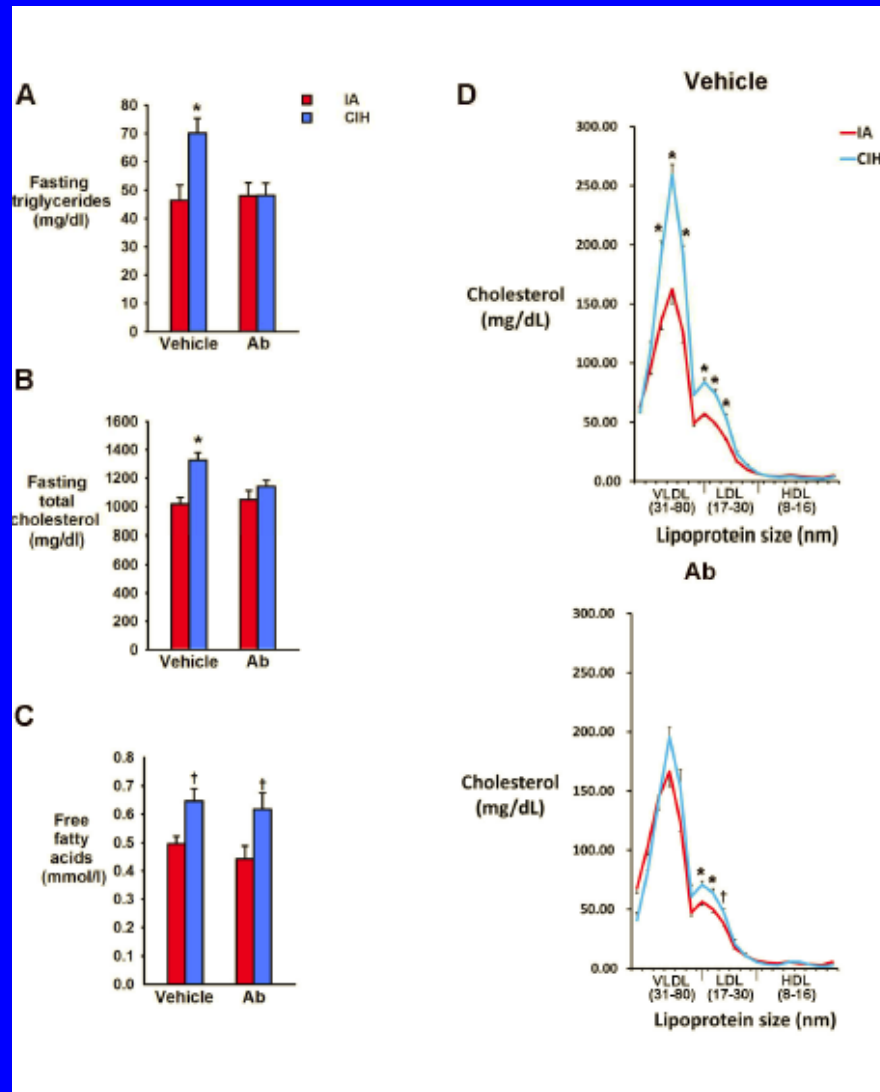
Shan L, Yu XC, Liu Z, Hu Y, Sturgis LT, Miranda ML, Liu Q. J Biol Chem. 2009 Jan 16;284(3):1419-24

Intermittent Hypoxia Increases Adipose Angptl4

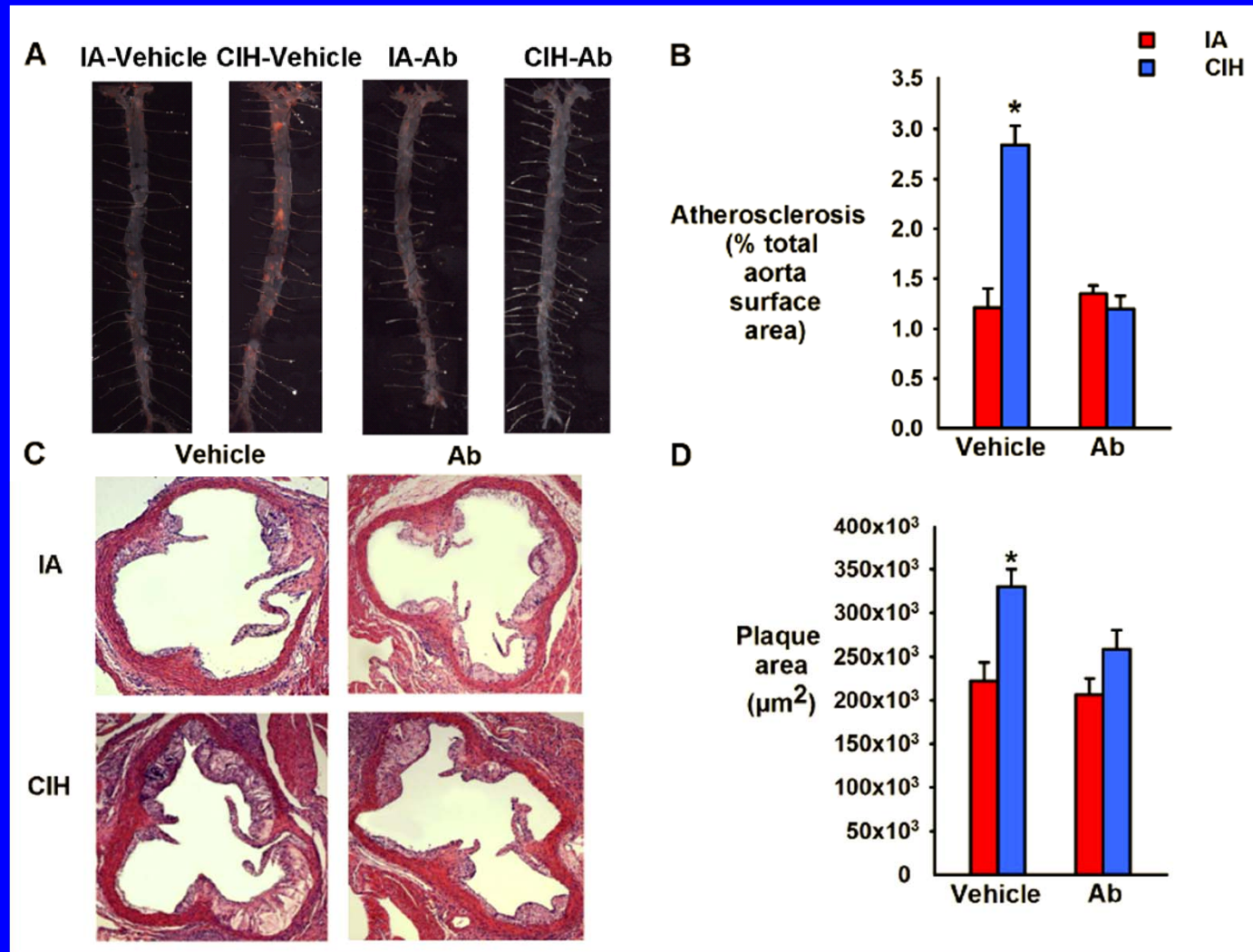


Drager et al. Eur Heart J . 2012; 33:783-90.

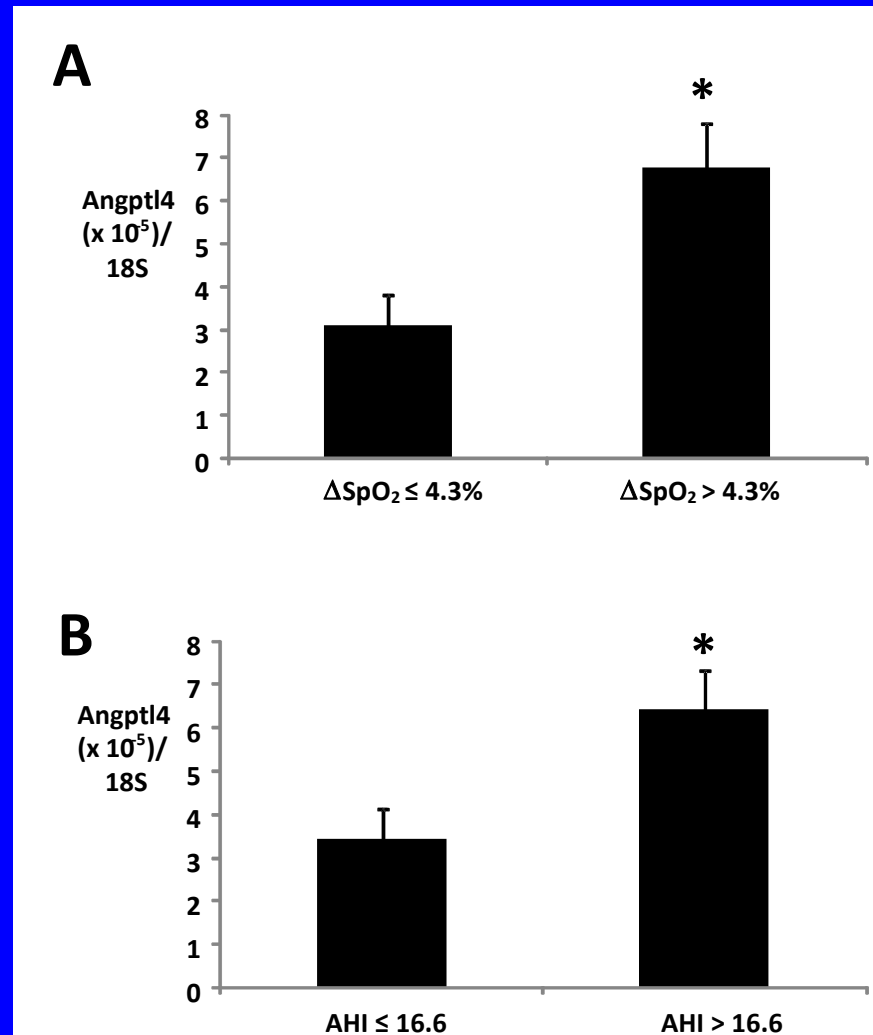
Angptl4 Ab prevent CIH-induced dyslipidemia



Angptl4 Ab prevent CIH-induced atherosclerosis



In obese patients, expression of Angptl4 in subcutaneous fat depended on the severity of hypoxemia and OSA

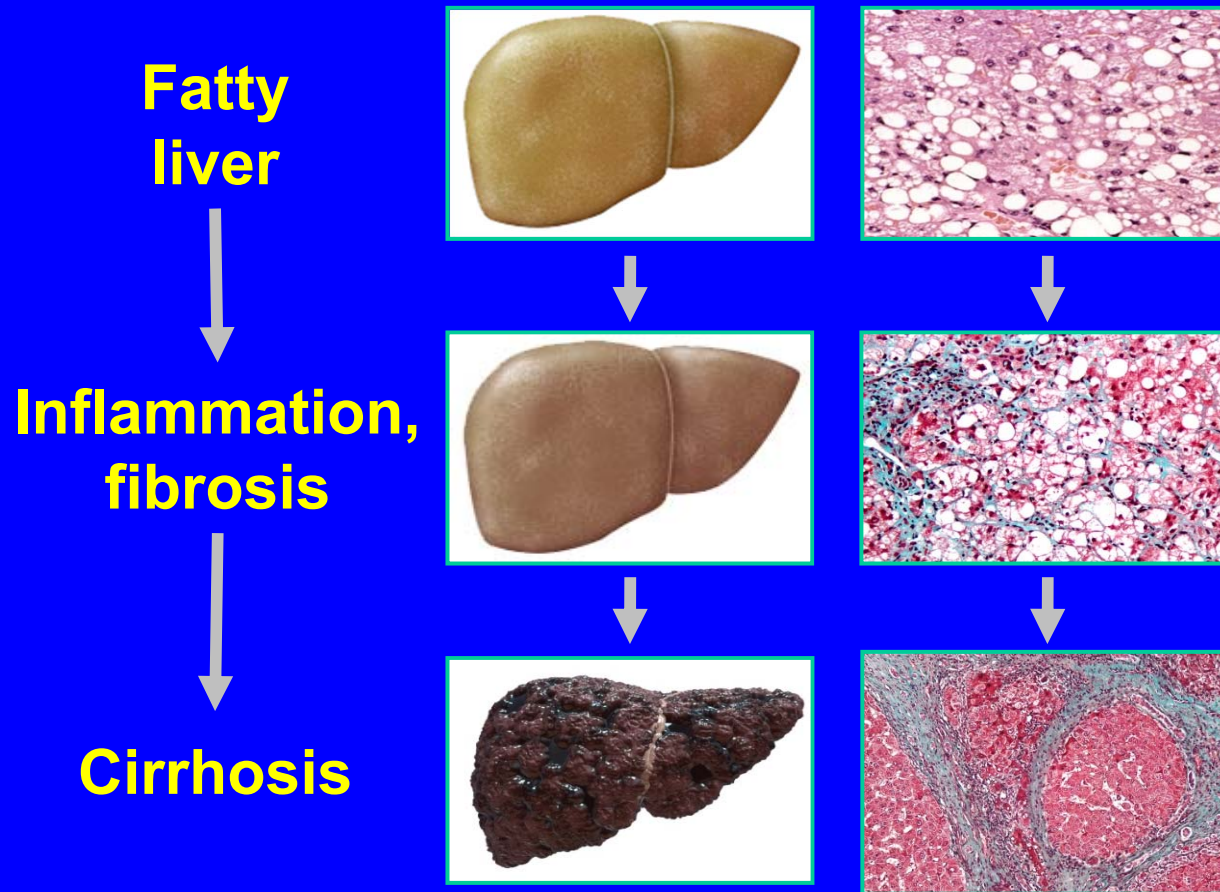


Intermittent Hypoxia and Lipoprotein Clearance

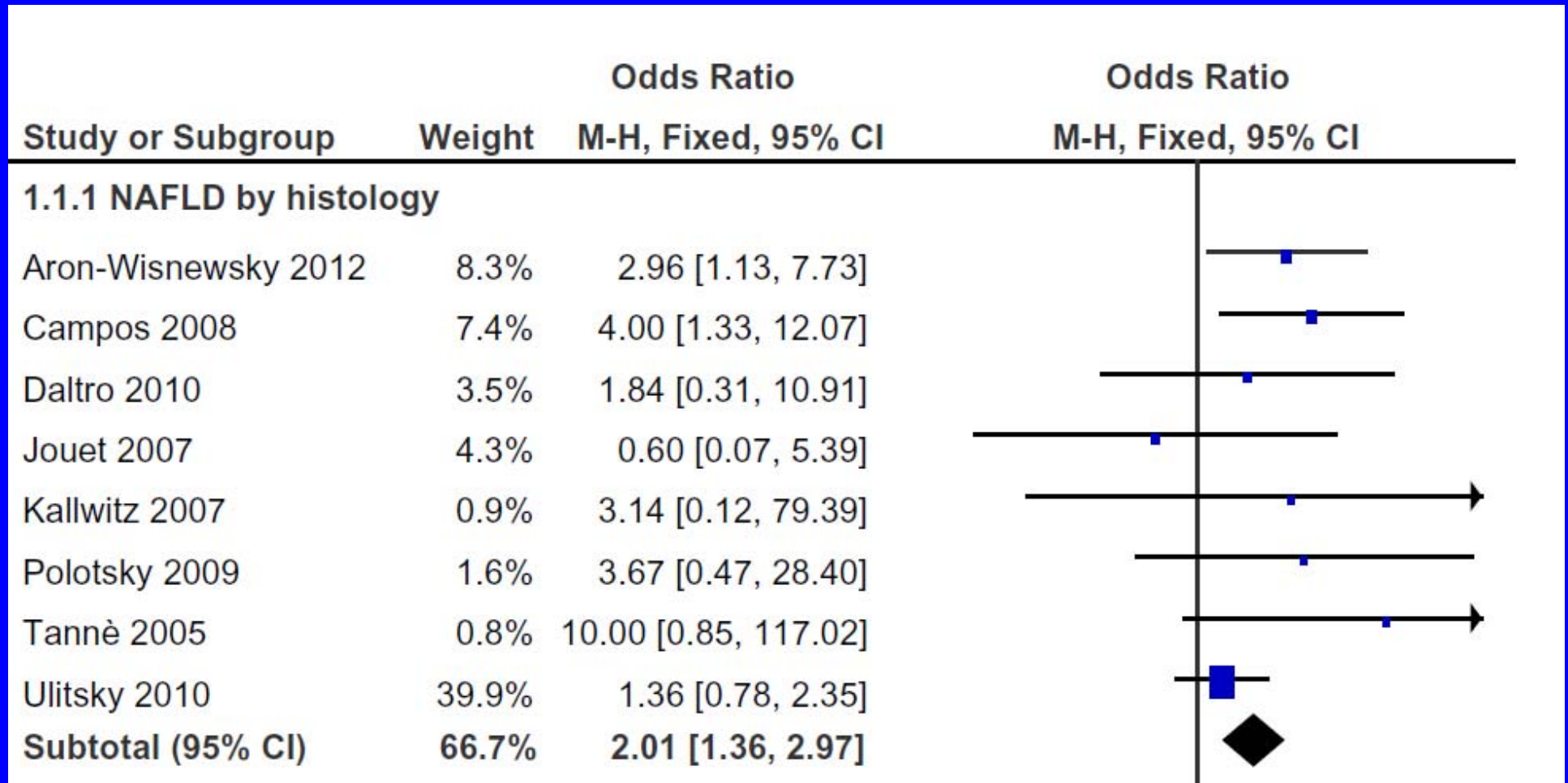
- ↓ Lipoprotein clearance by up-regulating adipose Angptl4, a potent inhibitor of lipoprotein lipase
- Adipose tissue hypoxia may play a role in cardiovascular morbidity and mortality of OSA

- **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

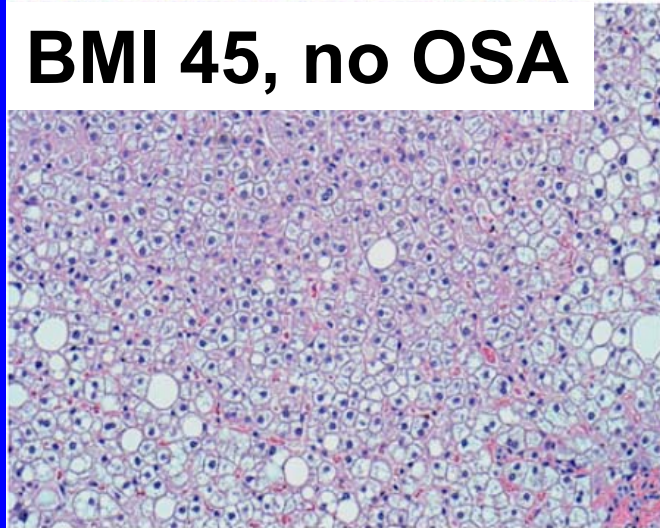


OSA and Non-Alcoholic Fatty Liver

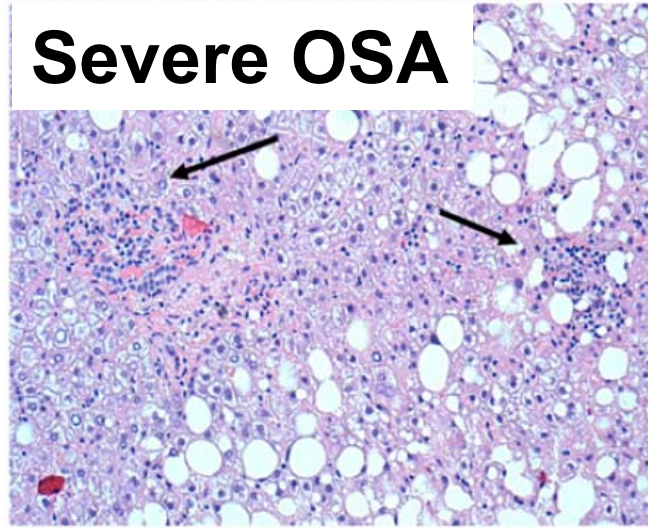


OSA and Non-Alcoholic Fatty Liver

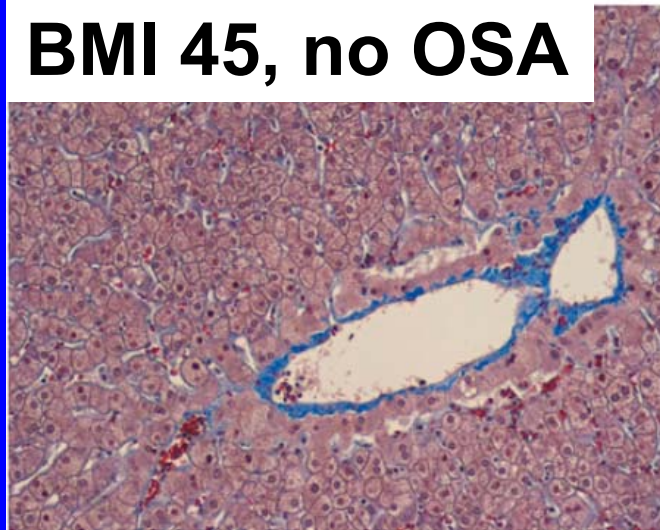
BMI 45, no OSA



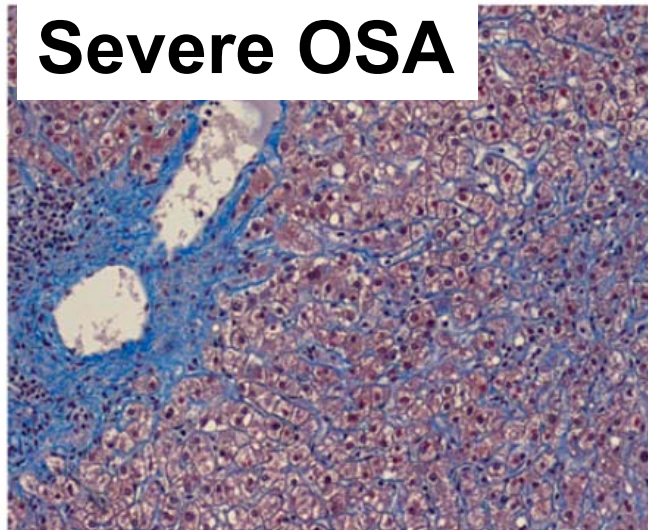
Severe OSA



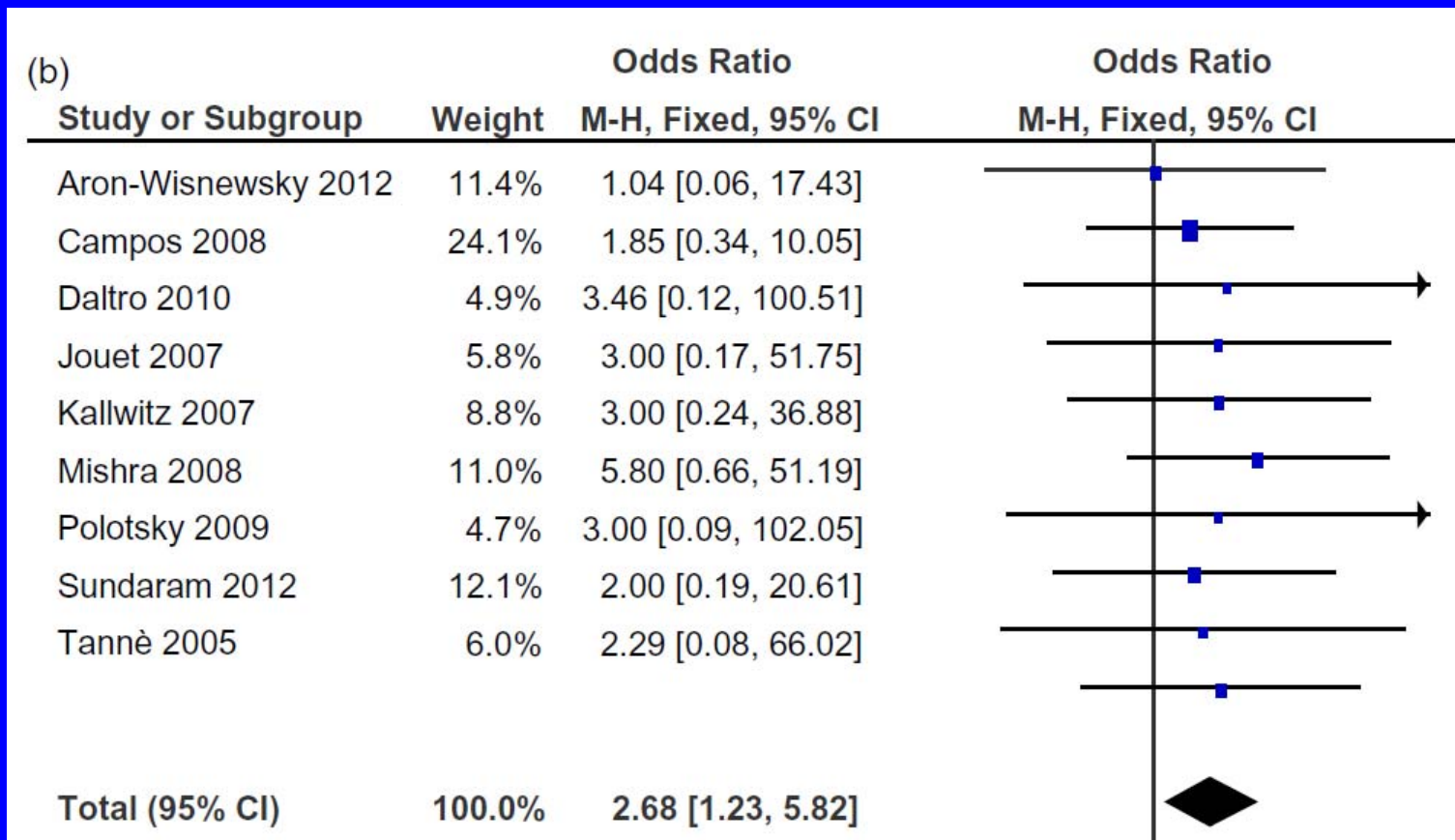
BMI 45, no OSA



Severe OSA



OSA and Non-Alcoholic Fatty Liver: Liver Fibrosis

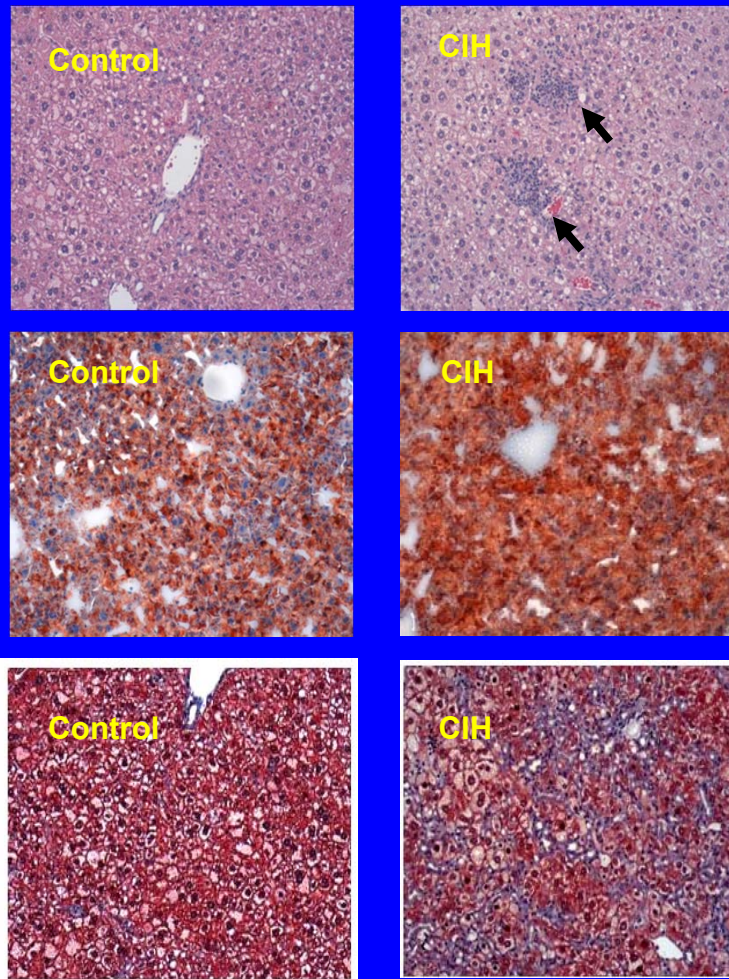


i has a cheezie



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Intermittent Hypoxia Causes Steatohepatitis and Liver Fibrosis



What are the mechanisms ?

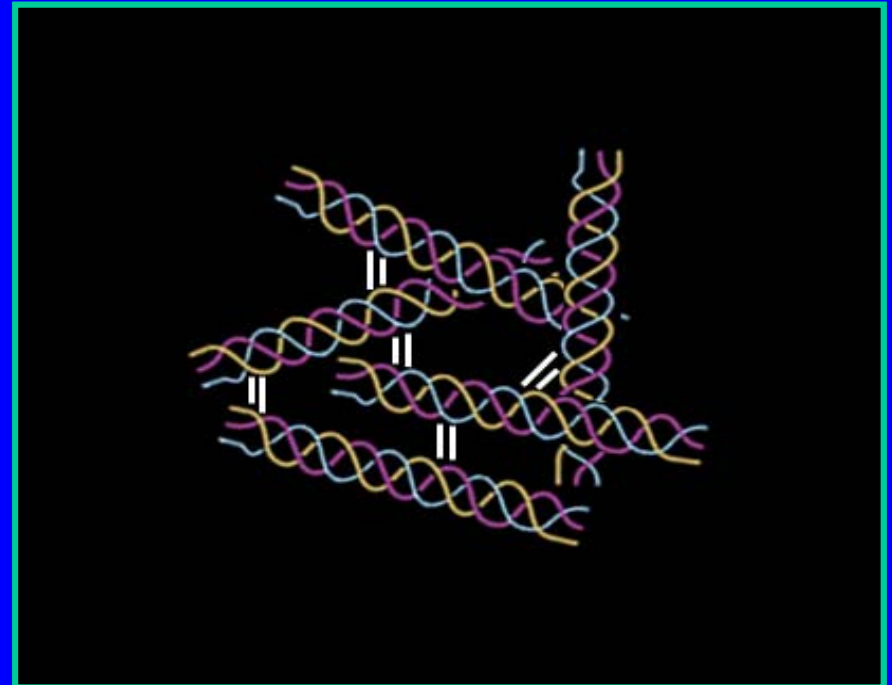


Lysyl oxidase (LOX)

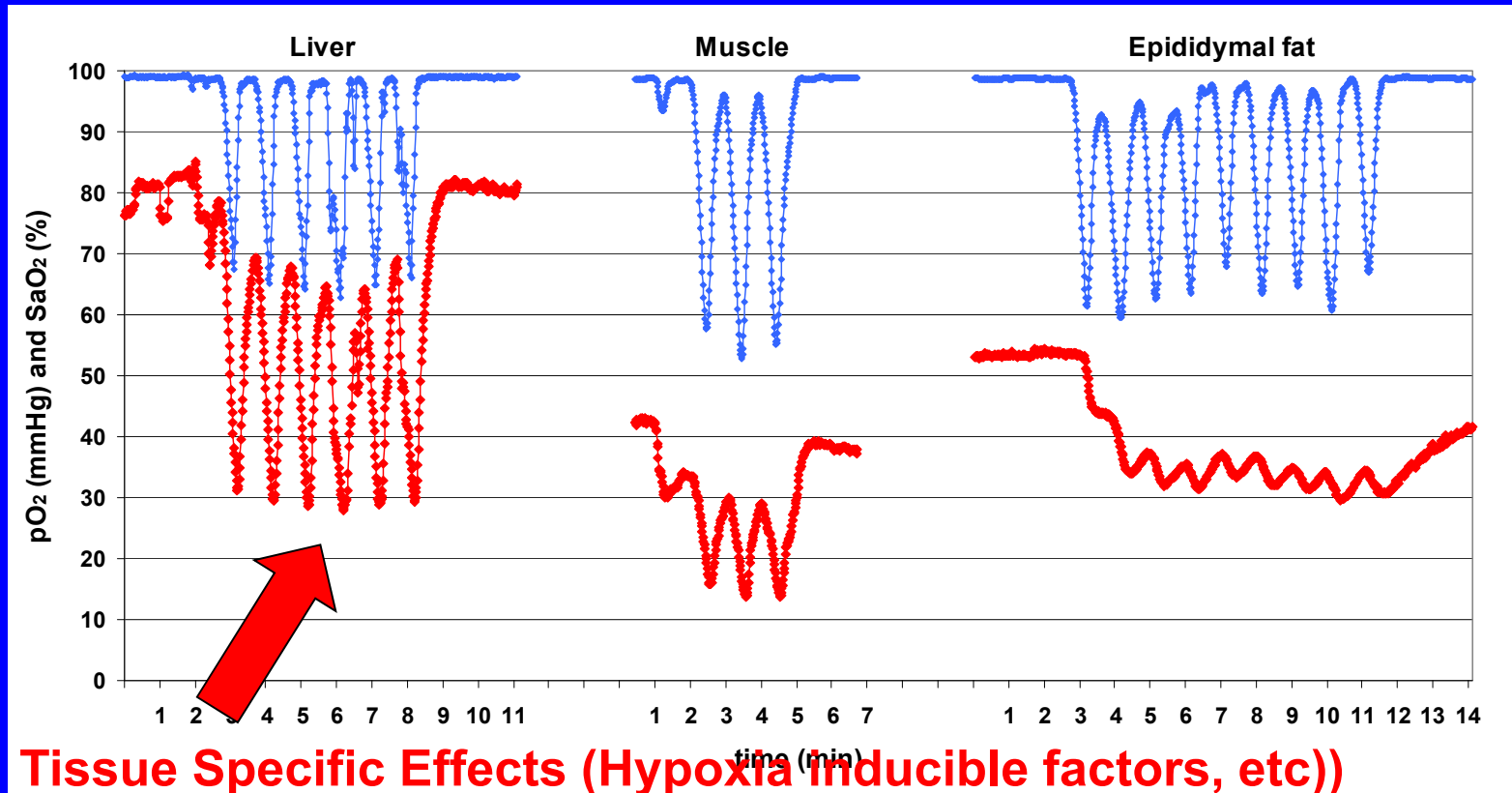
- Secreted amine oxidase.
- Catalyzes formation of covalent bonds between collagen fibers.
- Tissue hypoxia (via HIF-1) increases expression of LOX.

Kagan et al., 2003.

Erler et al., 2006; Higgins et al., 2007.

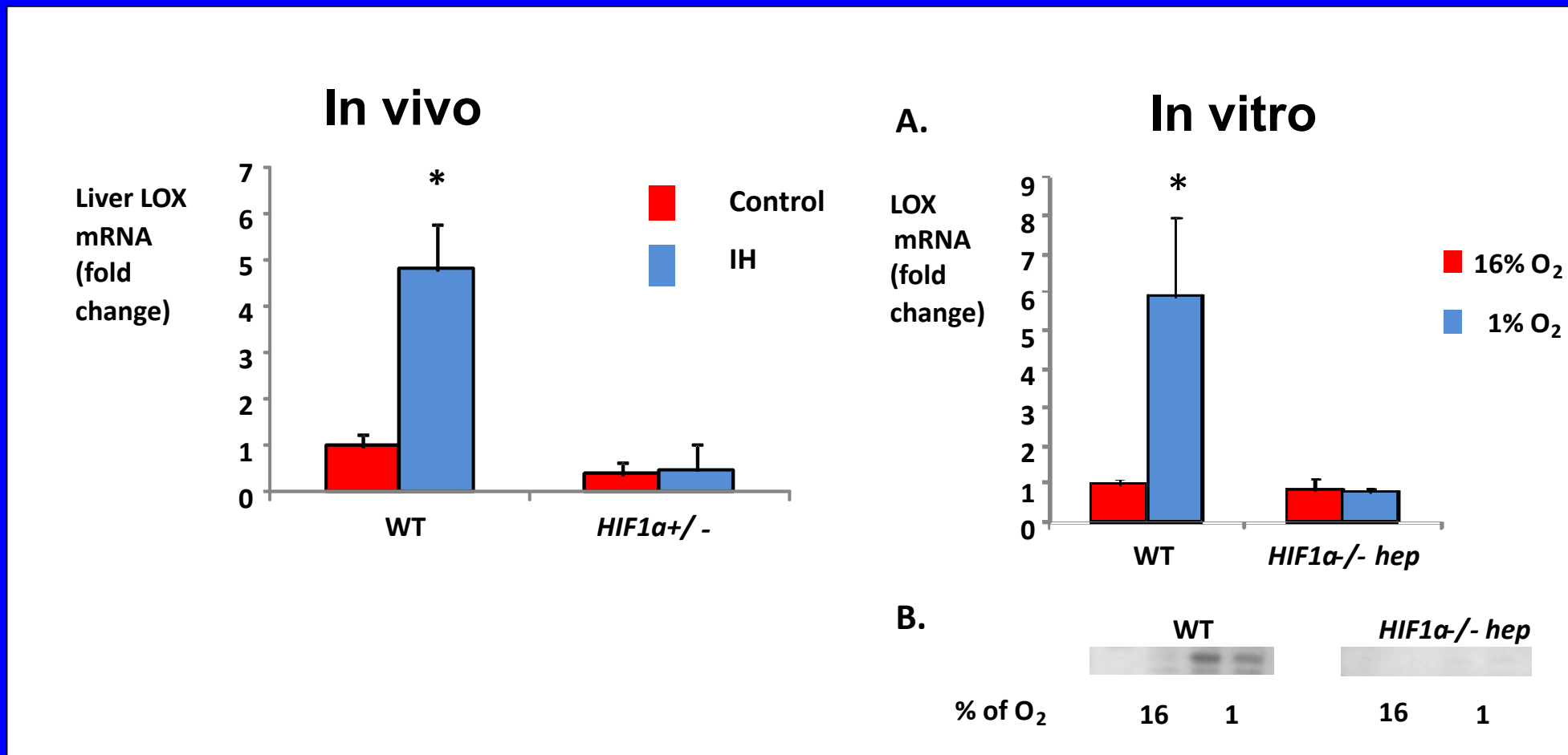


Mouse Model of Intermittent Hypoxia

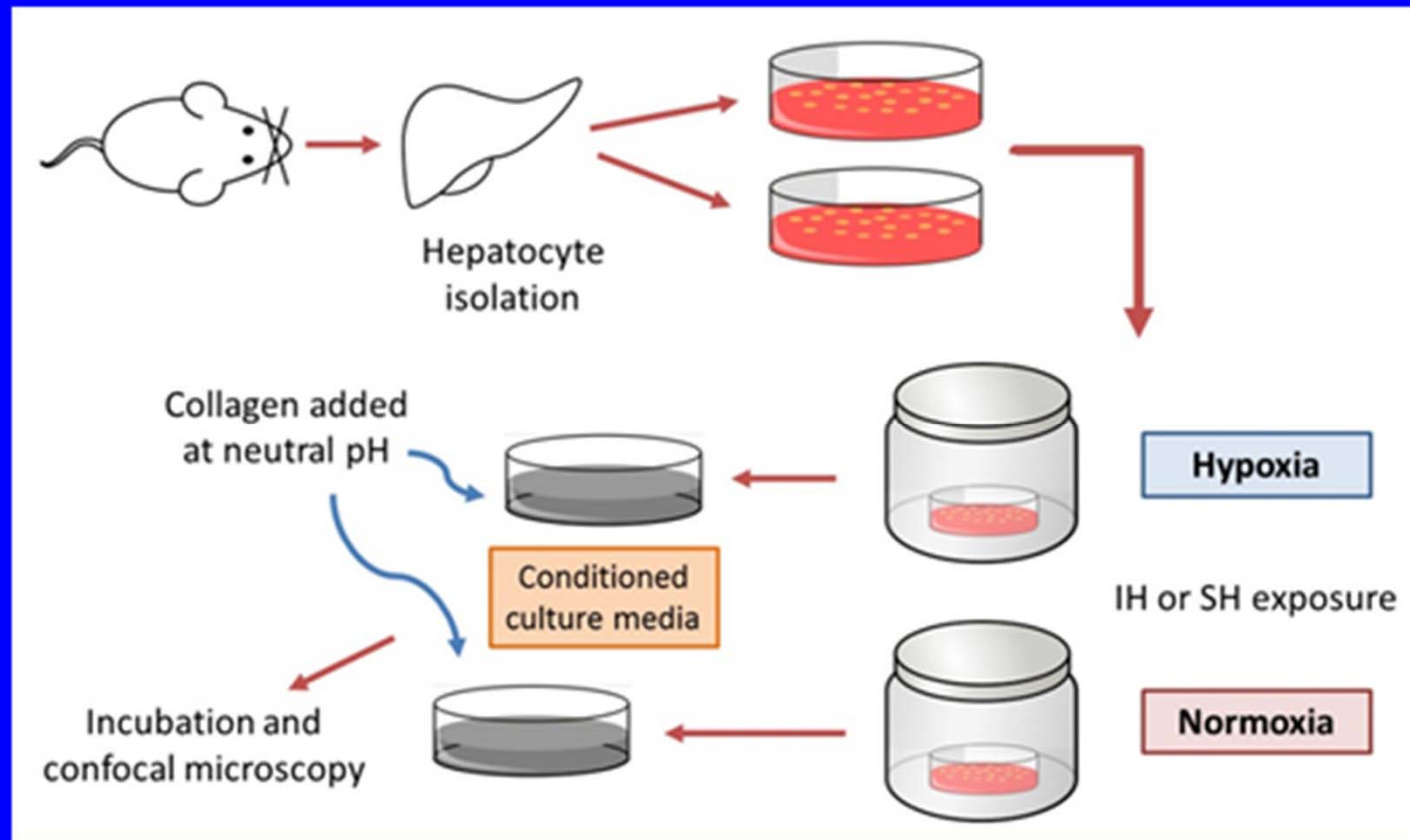


Tissue Specific Effects (Hypoxia inducible factors, etc)

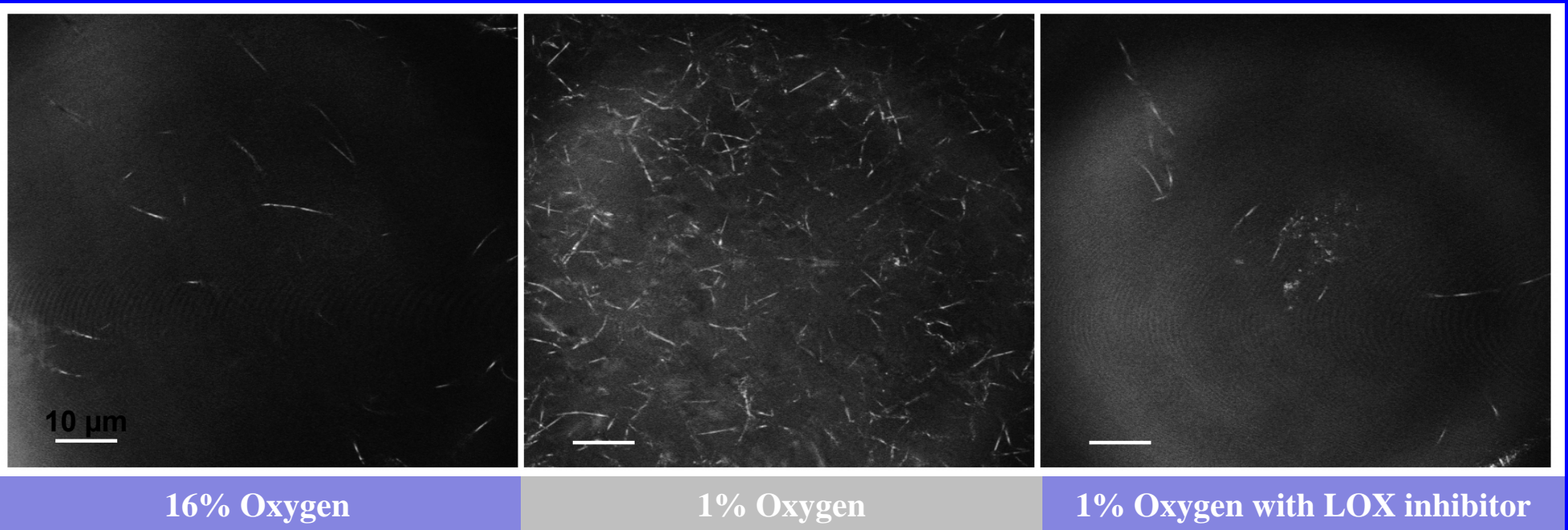
Intermittent hypoxia up-regulates collagen cross-linking enzyme lysyl oxidase in hepatocytes via hypoxia inducible factor 1 α



LOX secreted by hepatocytes in hypoxic cross-links collagen



LOX secreted by hepatocytes in hypoxic cross-links collagen

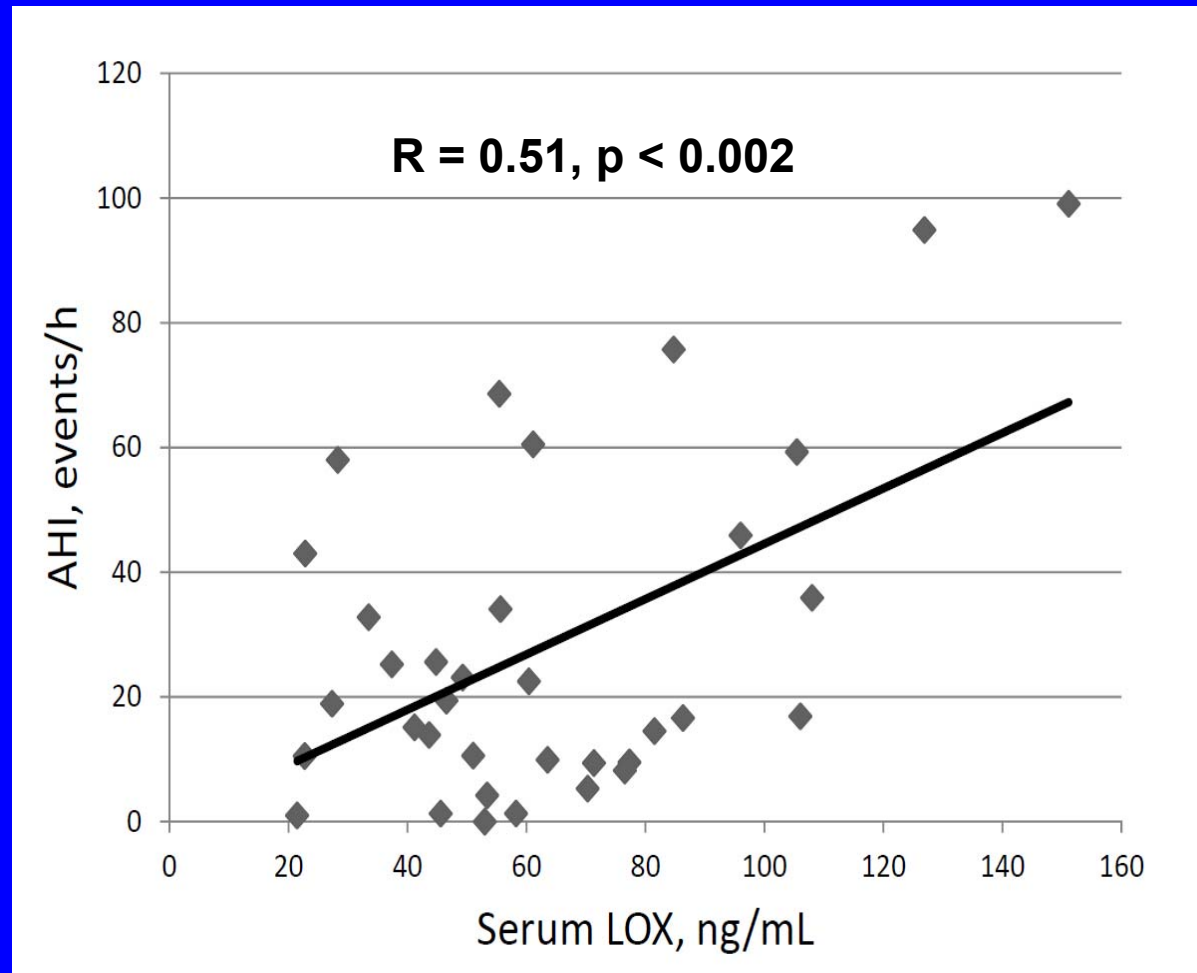


Mesarwi et al. Manuscript in preparation

Study design

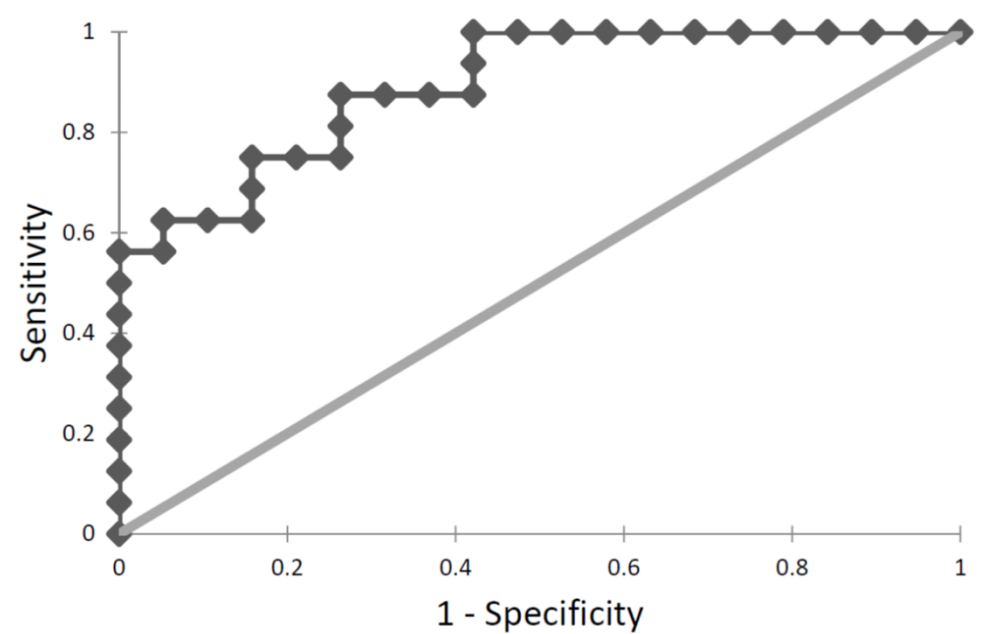
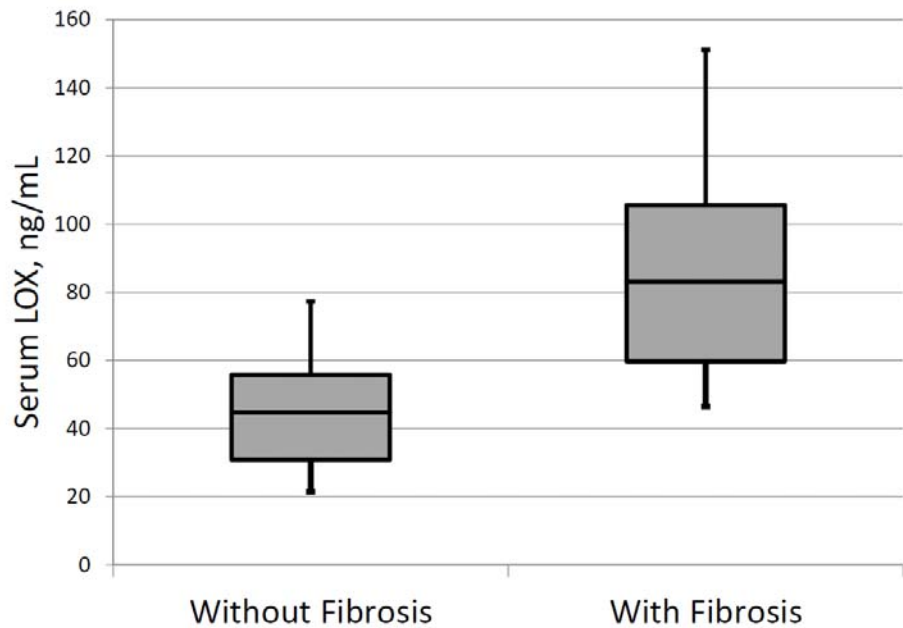
- 35 consecutive patients recruited from the Bariatric Surgery clinic at Johns Hopkins Bayview Medical Center.
- Polysomnogram
- Serum LOX checked the morning after PSG.
- Liver biopsies analyzed for steatosis, fibrosis, and NAFLD activity score.
- Patients categorized by presence/absence of hepatic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

OSA → IH → LOX → Liver Fibrosis



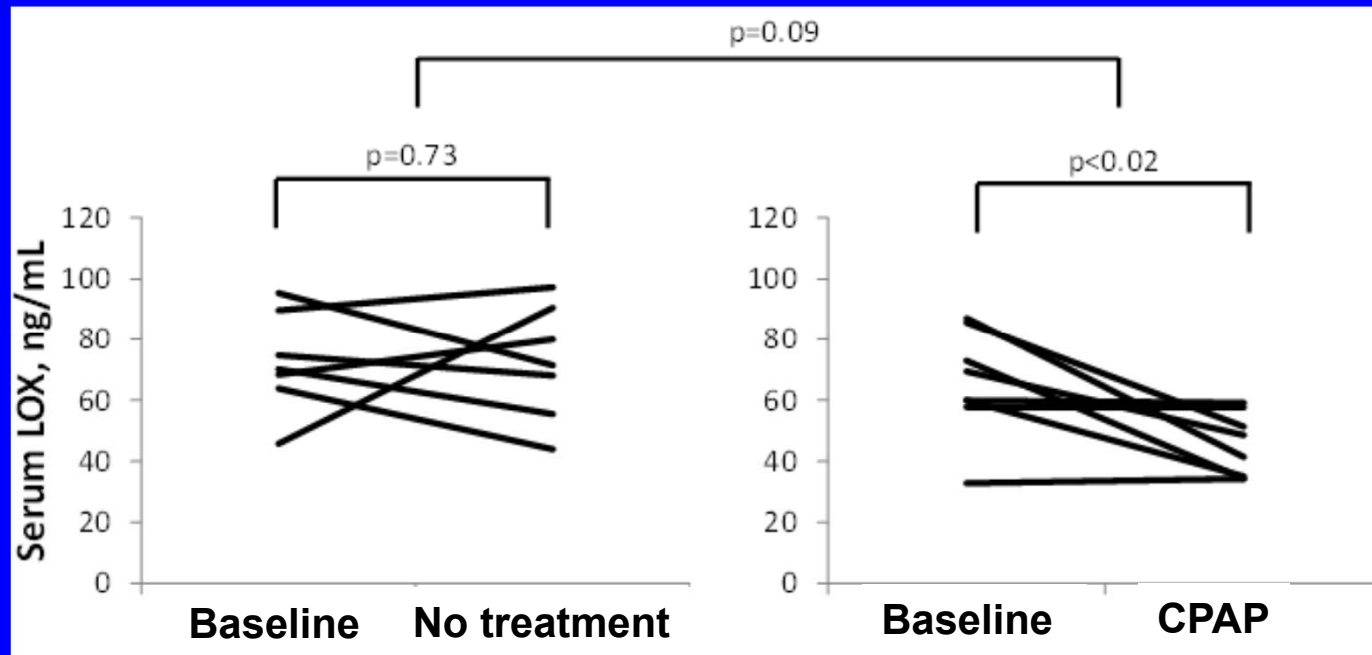
Mesarwi et al. Manuscript in preparation

OSA → IH → LOX → Liver Fibrosis



Mesarwi et al. Manuscript in preparation

OSA → IH → LOX → 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-1 α**
- 3. HIF-1 α up-regulates LOX**
- 4. LOX cross-links collagen resulting in liver fibrosis**

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AHA: 10GRNT3360001
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