The biomarker of endothelium damage in obstructive sleep apnea

莊立邦

Li-Pang Chuang MD; PhD.

林口長庚醫院 胸腔內科 主治醫師

桃園長庚醫院 睡眠中心 主任

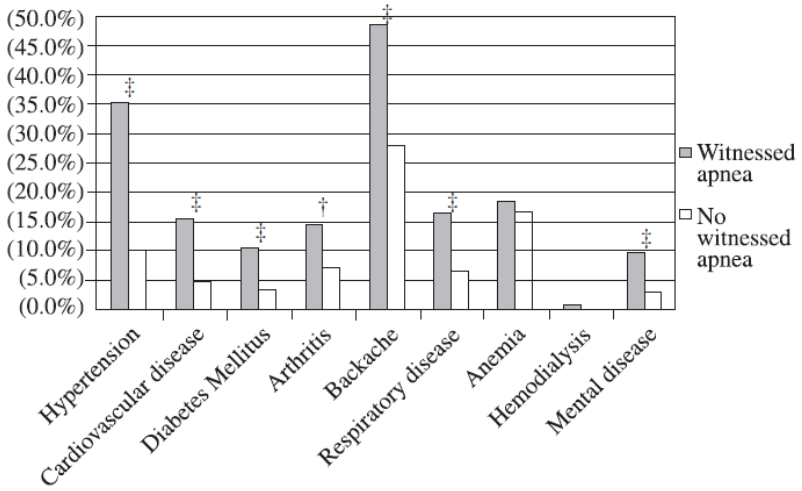
長庚大學 醫學系 助理教授

2019-12-08

Outline

- Endothelium damage in obstructive sleep apnea
- Biomarkers of endothelium damage
  - Cardiovascular
  - Renal

Comorbid of OSA



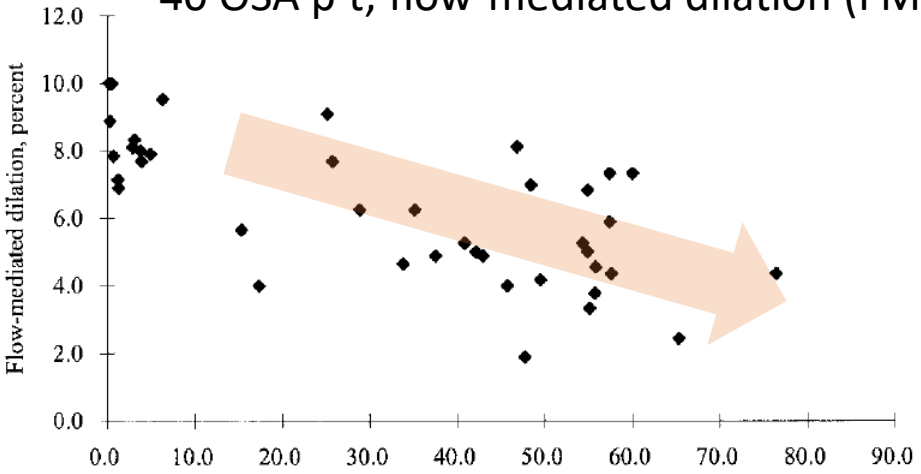
*: $p < 0.05$; †: $p < 0.01$; ‡: $p < 0.001$

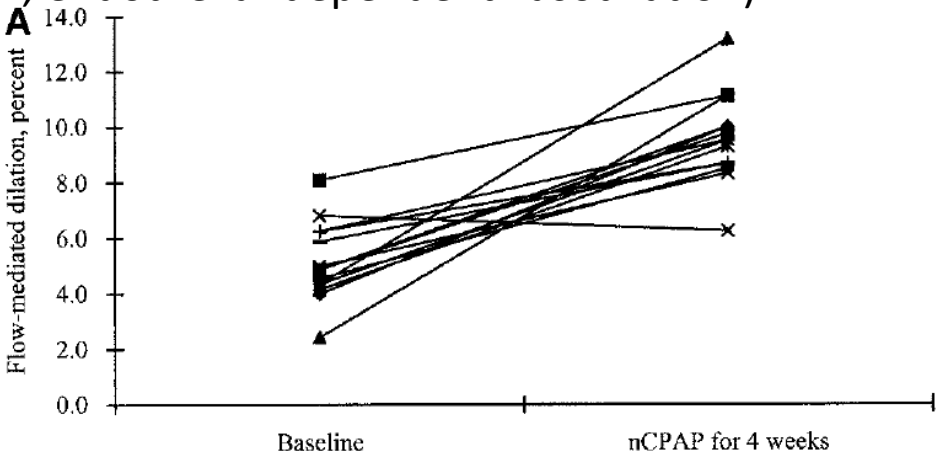
Materiale Plastice 2017;54(2)

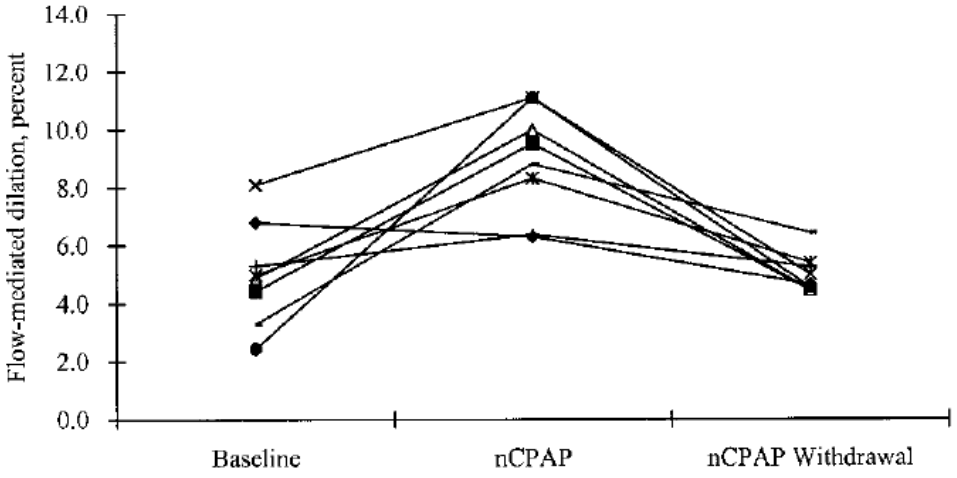
Chuang LP, et al. *Chang Gung Med Journal* 2008;311,77-83.

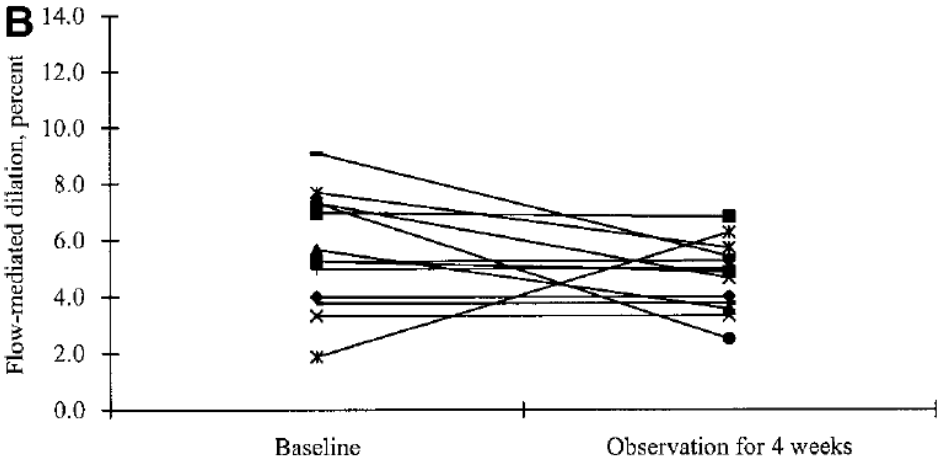
Endothelial function in OSA and response to treatment

- 40 OSA p't; flow-mediated dilation (FMD, endothelial-dependent vasodilation)





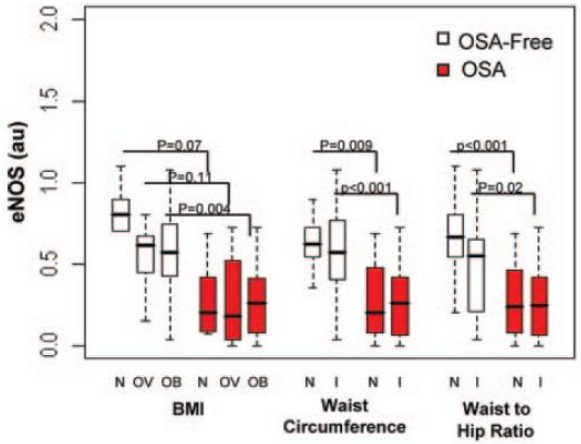


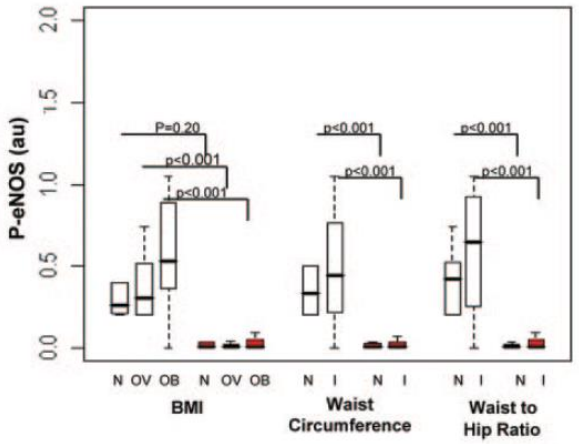


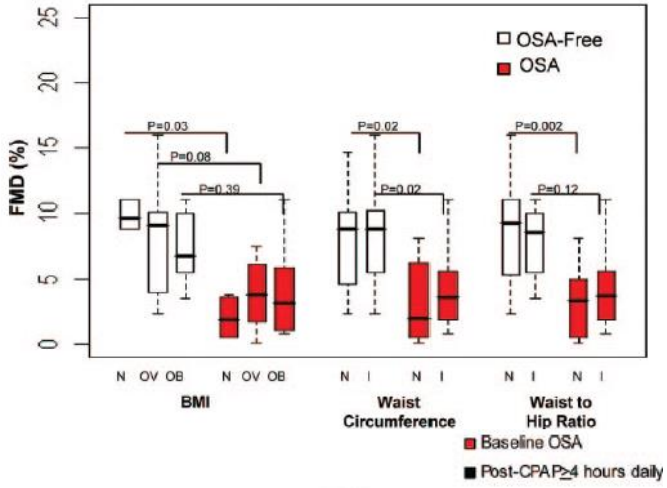
Mary S. M. Ip, et al. *Am J Respir Crit Care Med*. 2004 Feb 1;169:348-53

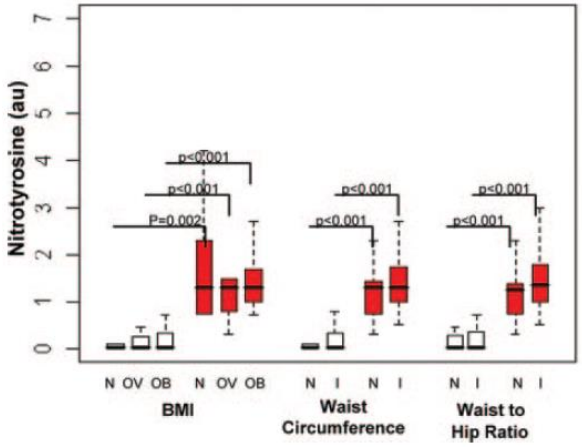
Vascular Inflammation in Obesity and Sleep Apnea

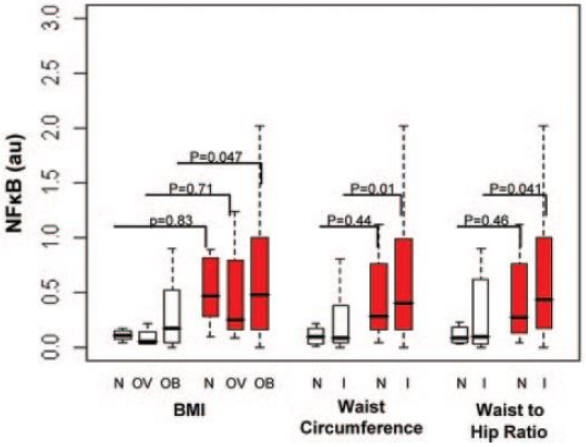
- 38 OSA vs 33 OSA-free obese p't;
- Vascular endothelial cell from peripheral vein (J-shaped vascular guidewires)

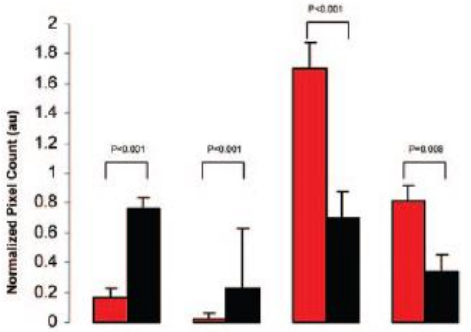








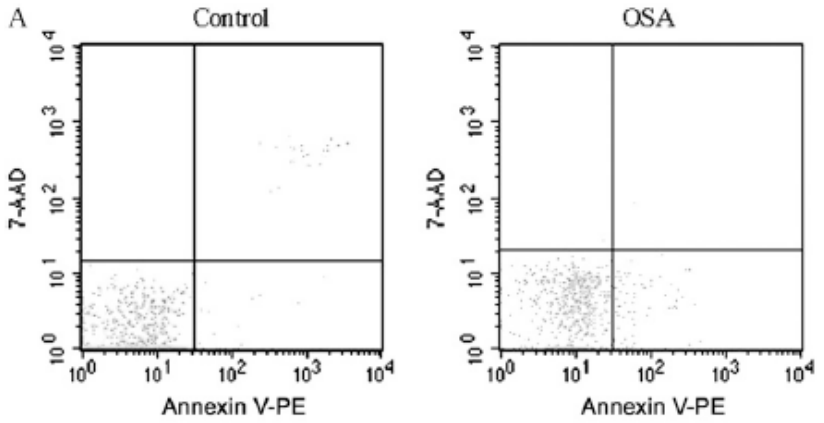


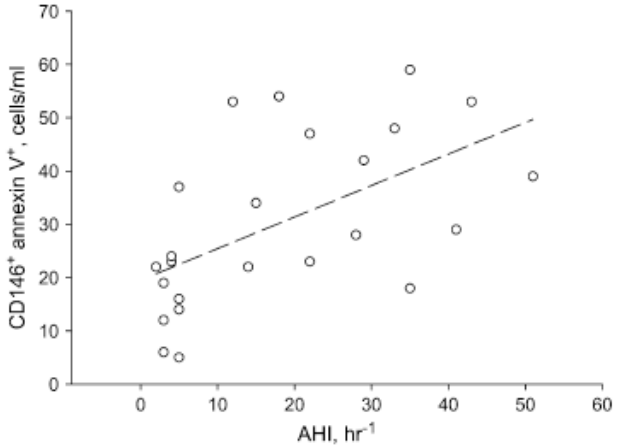


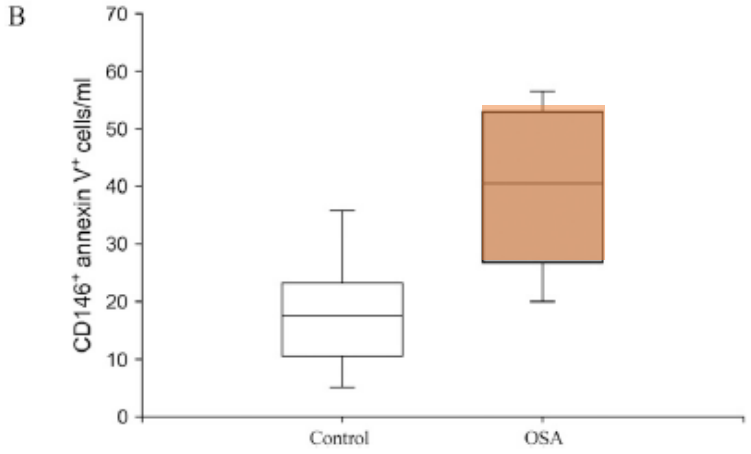
Circulation. 2010;121:1014-1021.

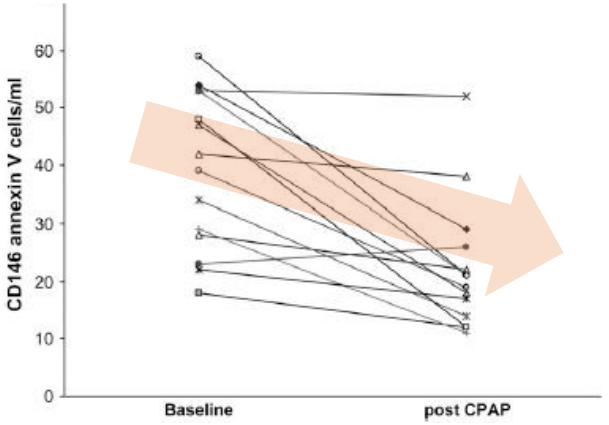
Endothelial Cell Apoptosis in Obstructive Sleep Apnea

- 14 OSA with 10 control; 8 weeks CPAP;
- FMD + circulating apoptotic endothelial cells (Ficoll-Hypaque+CD146)



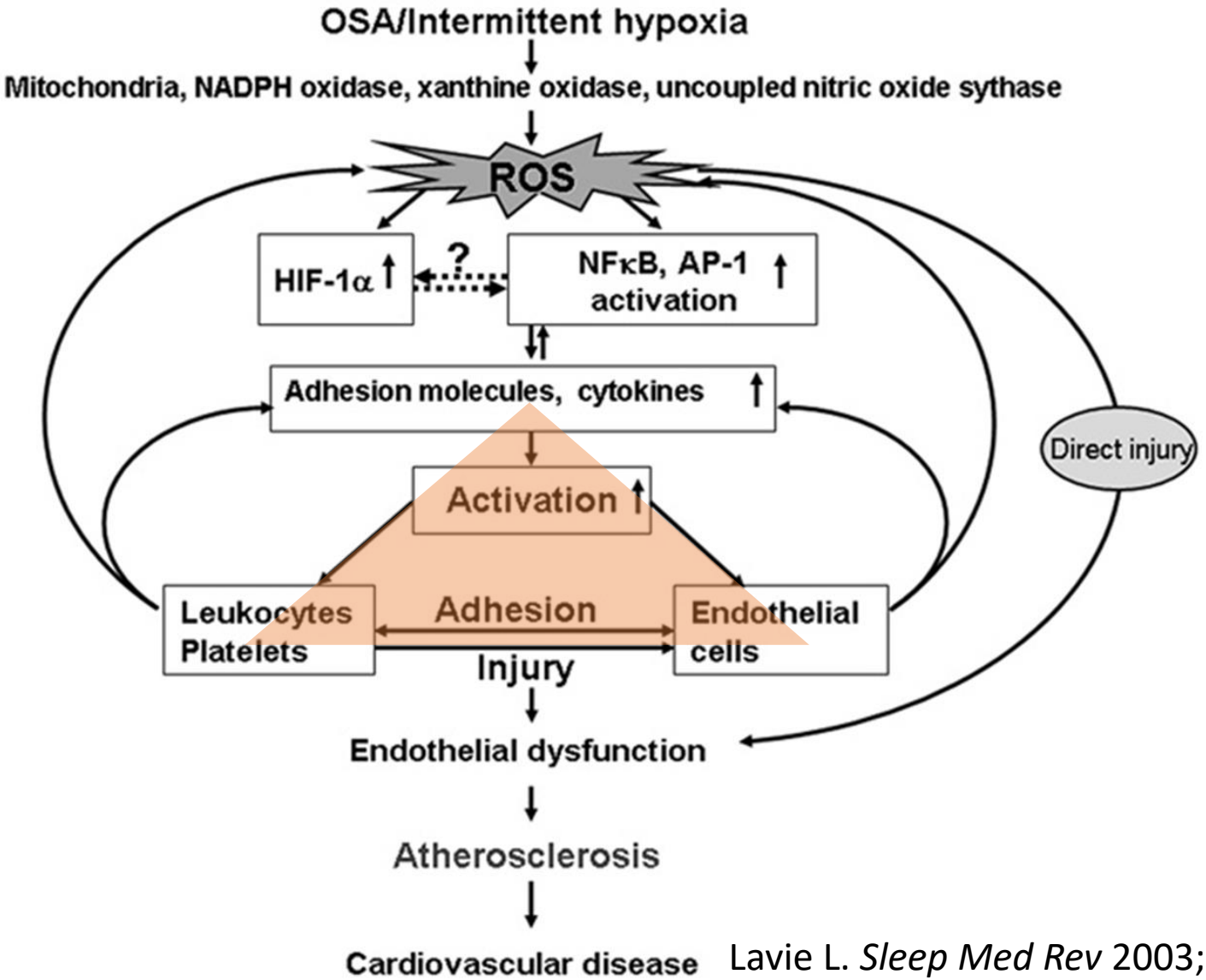






Am J Respir Crit Care Med. 2007;175(11):1186-91.

Pathophysiology of intermittent hypoxia

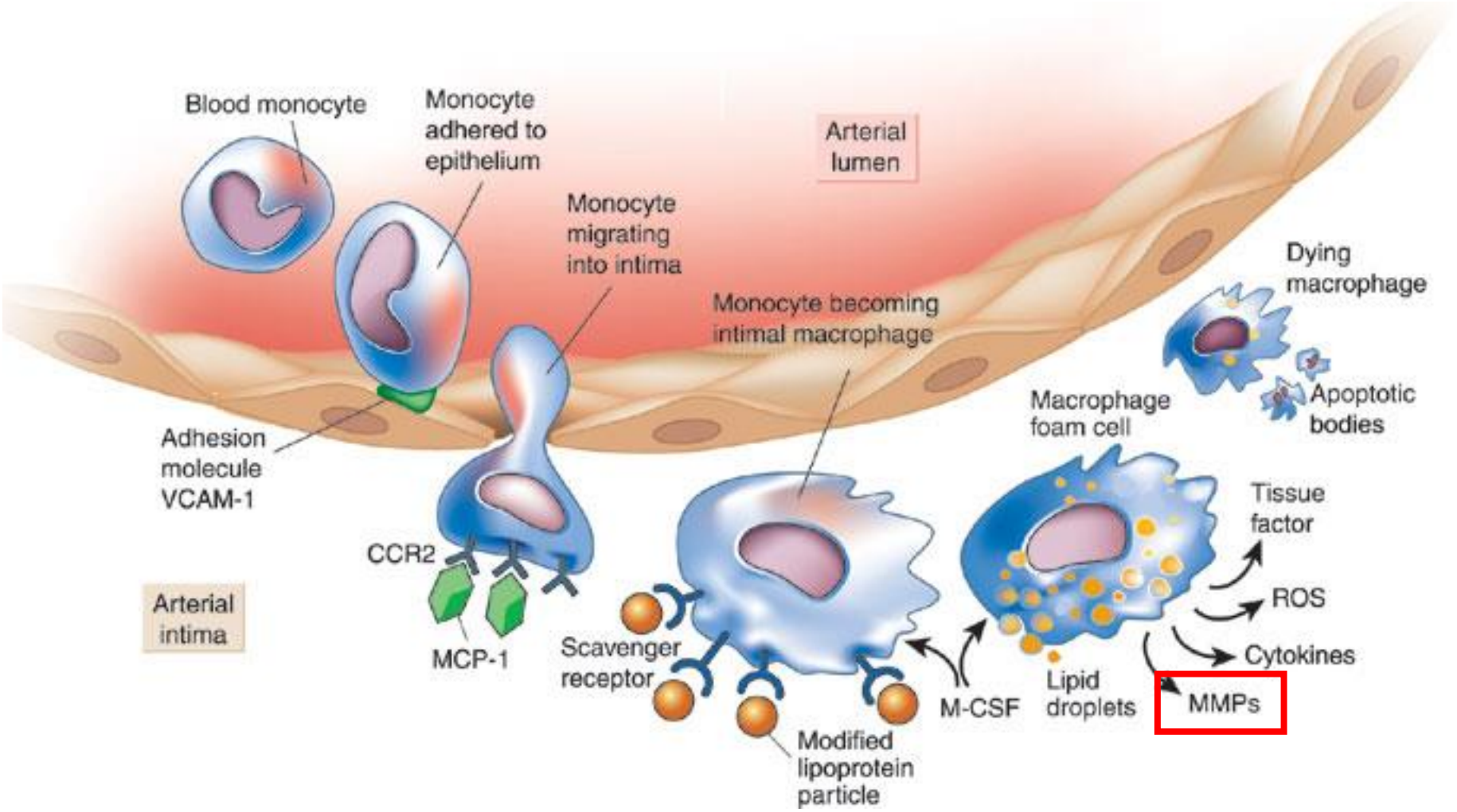


Lavie L. *Sleep Med Rev* 2003; 7:35-51

Outline

- Endothelium damage in obstructive sleep apnea
- Biomarkers of endothelium damage
  - Cardiovascular
  - Renal

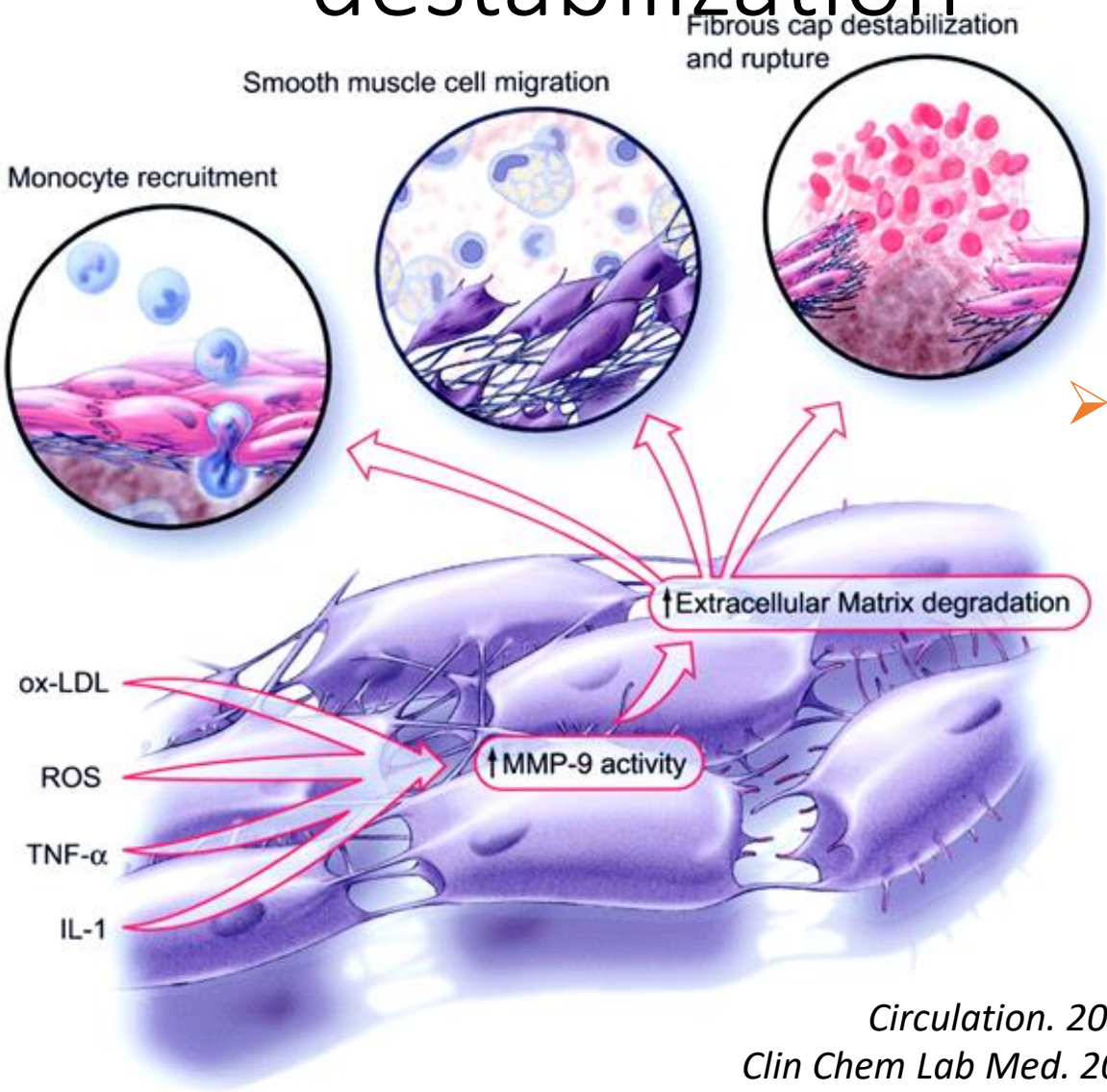
Monocytes, Endothelium, Inflammation and Atherosclerosis



Circulation. 1993 Aug;88(2):358-63.

Nature. 2002 Dec;420:868-874.

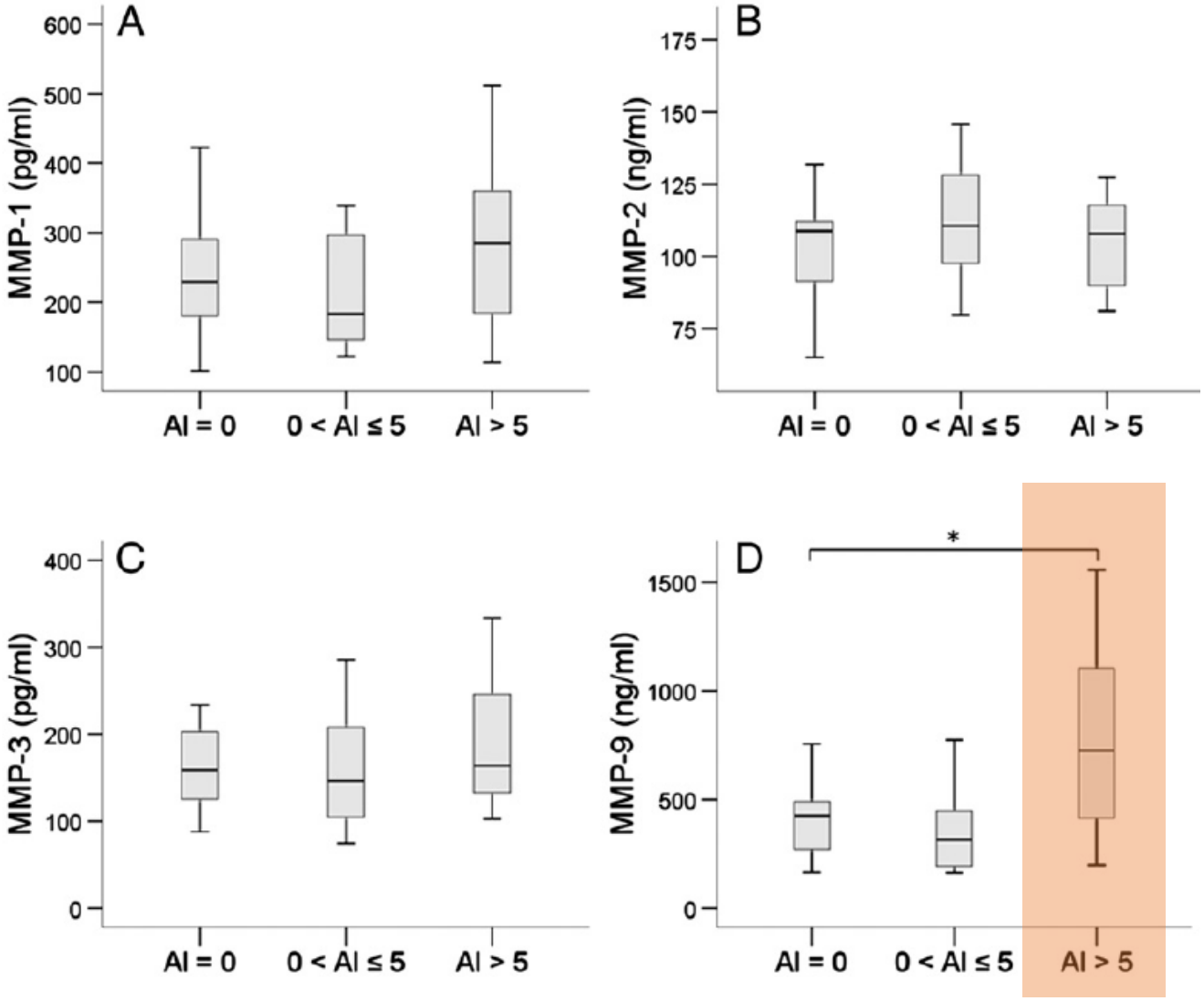
MMP, from plaque progression to destabilization



- **MMP-9 is a predictor of cardiovascular mortality in CAD**

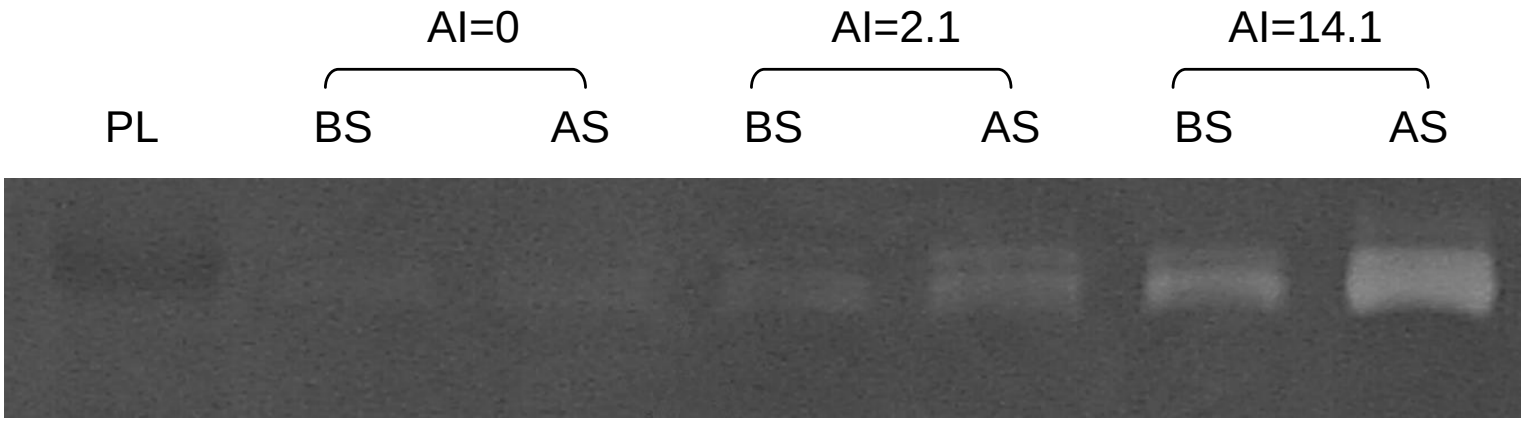
Circulation. 2003 Apr 1;107(12):1579-85.
Clin Chem Lab Med. 2017 Nov 27;56(1):147-156.

Plasma MMP-9 changes & Monocyte MMP-9 RNA expression in OSA patients

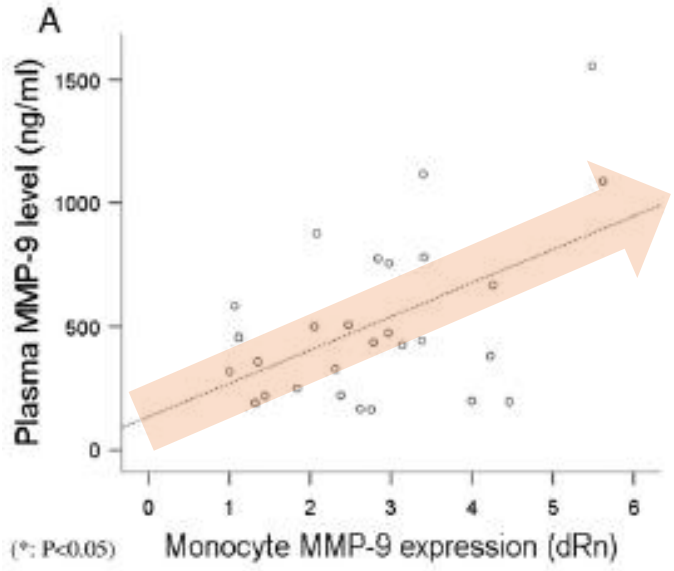


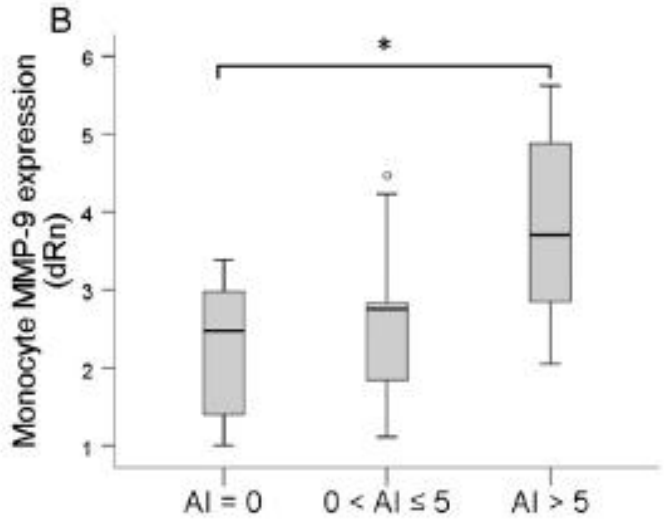
LP Chuang et al. *Life Sciences* 93 (2013) 220–225

Plasma MMP-9 changes & Monocyte MMP-9 RNA expression in OSA patients



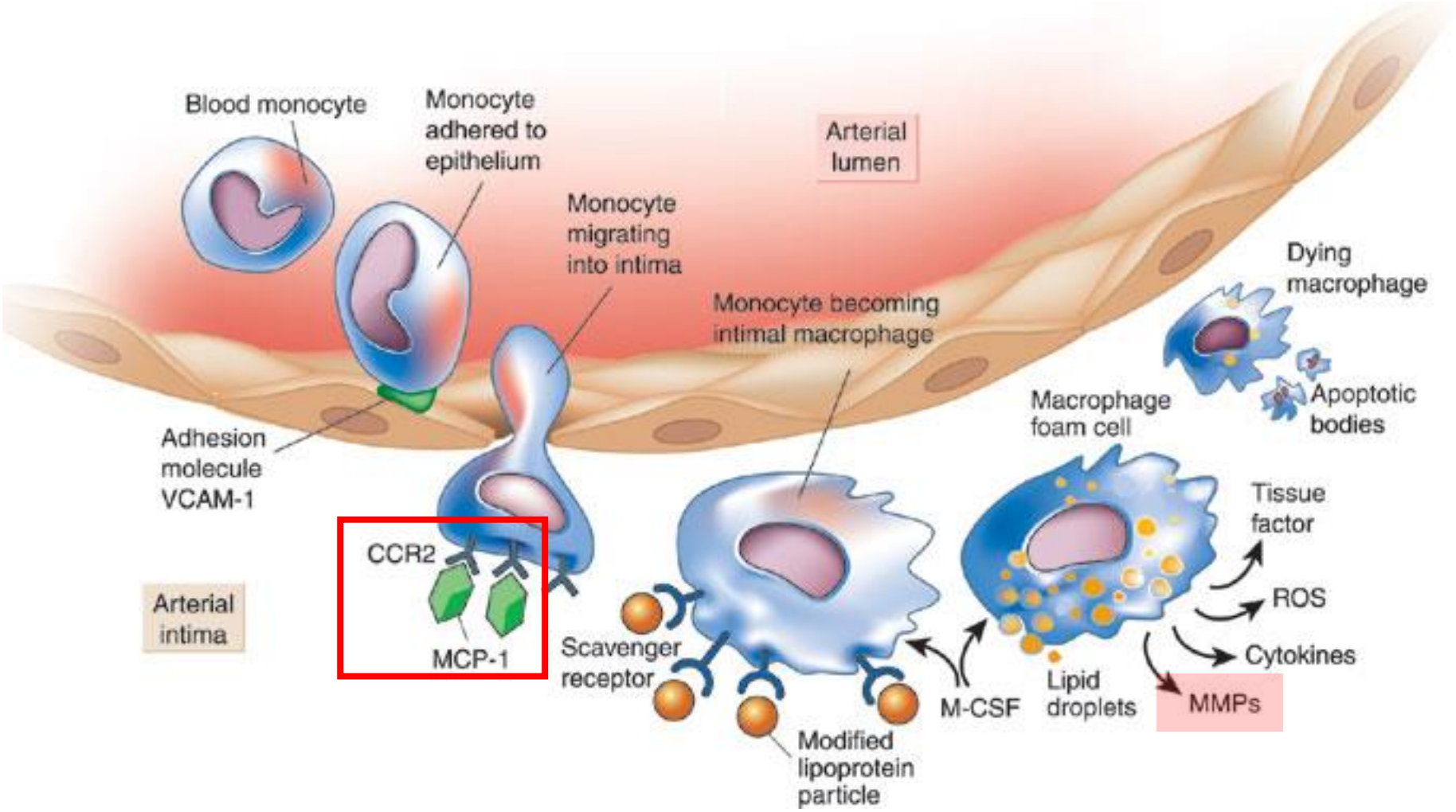
PL: protein leader; AI: apnea index; BS: before sleep; AS: after sleep





LP Chuang et al. *Life Sciences* 93 (2013) 220–225

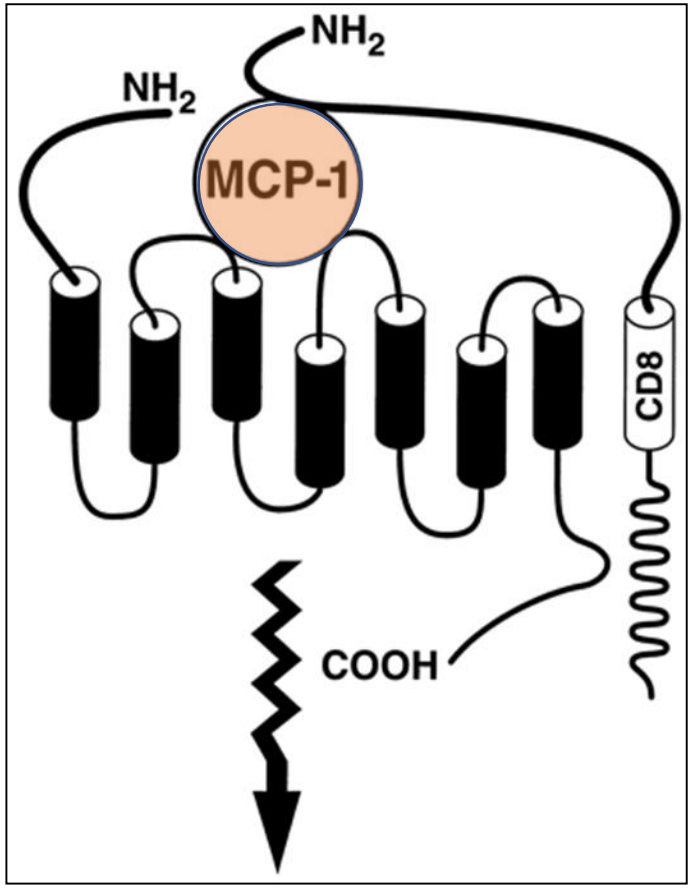
Monocytes, Endothelium, Inflammation and Atherosclerosis

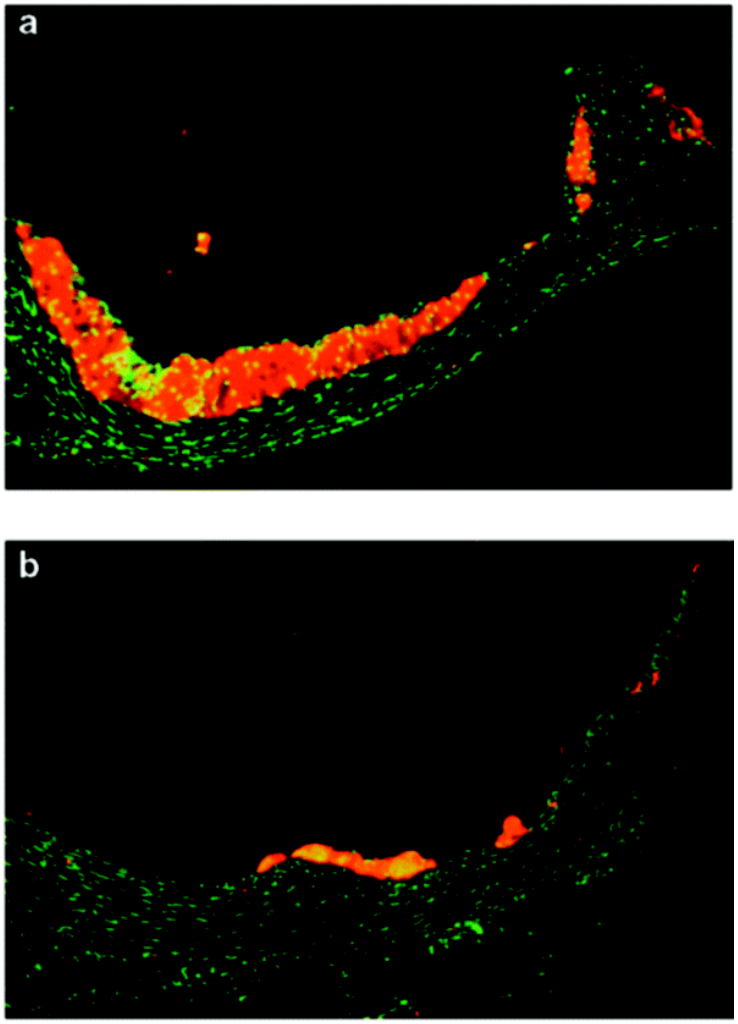


Circulation. 1993 Aug;88(2):358-63.

Nature. 2002 Dec;420:868-874.

Chemokine Receptor 2(CCR2) and MCP-1

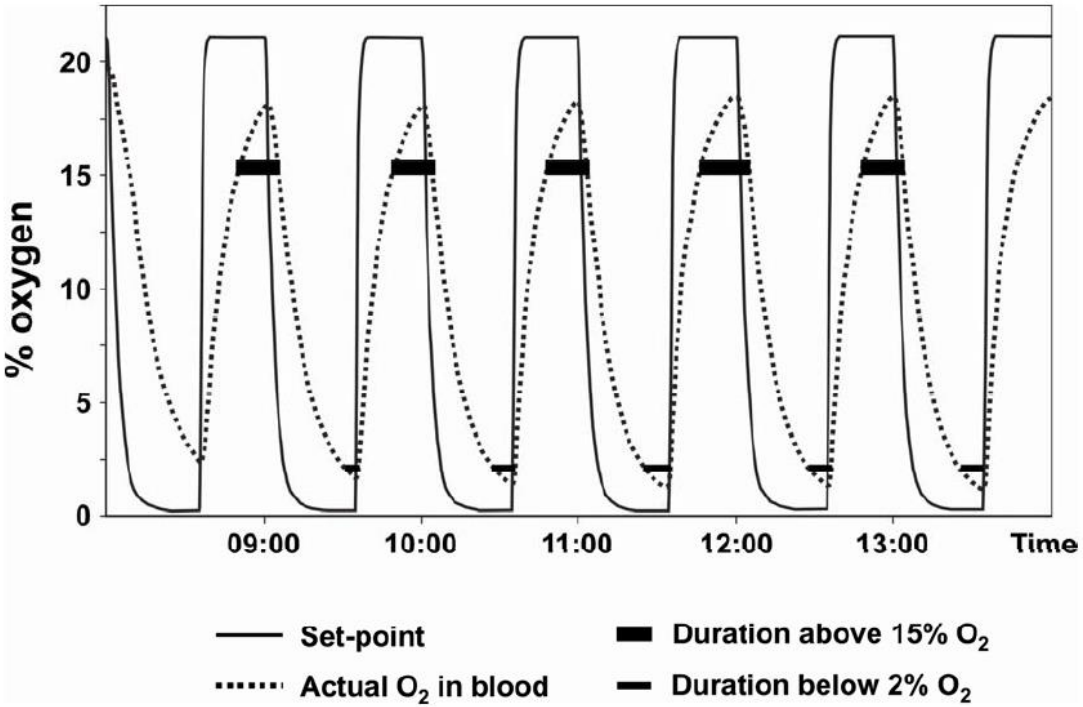




- CCR2(-/-) mice show defect in monocyte recruitment and ↓ atherosclerotic

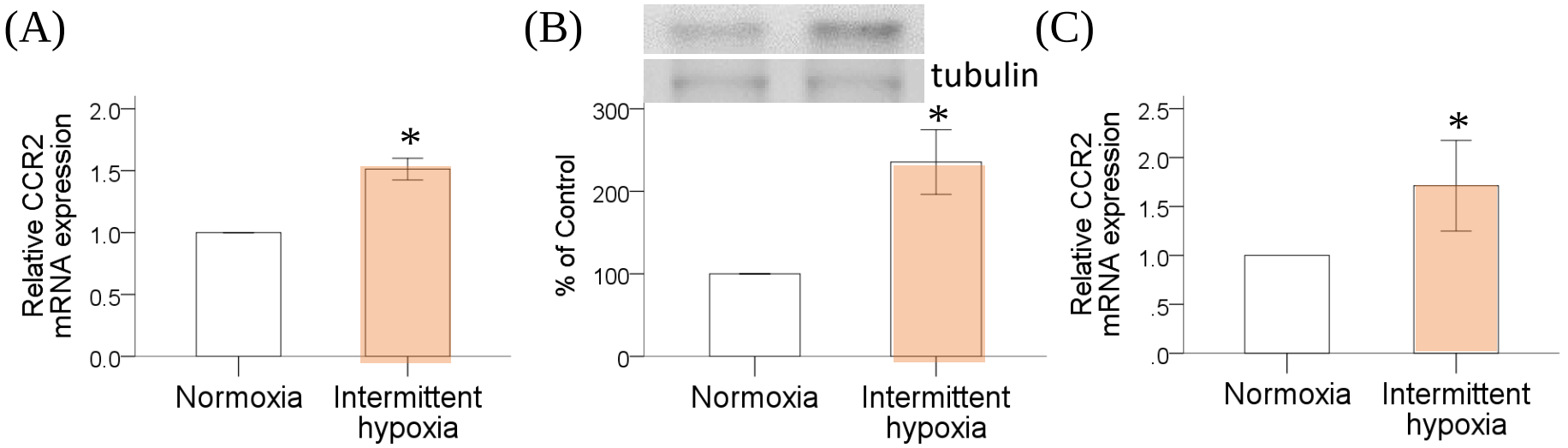
Nature. 1998 Aug 27;394(6696):894-7

Intermittent hypoxia culture system



Lavie L. *Am J Respir Crit Care Med* 2008; 177(5): 544-554.

IH ↑ CCR2 mRNA expression(A) and membrane protein(B) in THP-1 cells & human monocyte(C)

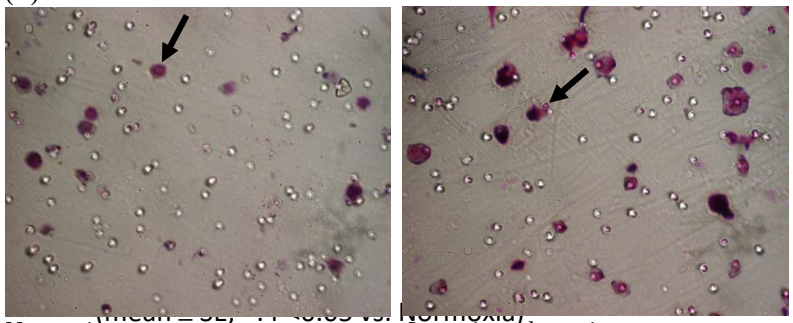


(mean ± SE, *: P<0.05 vs. Normoxia).

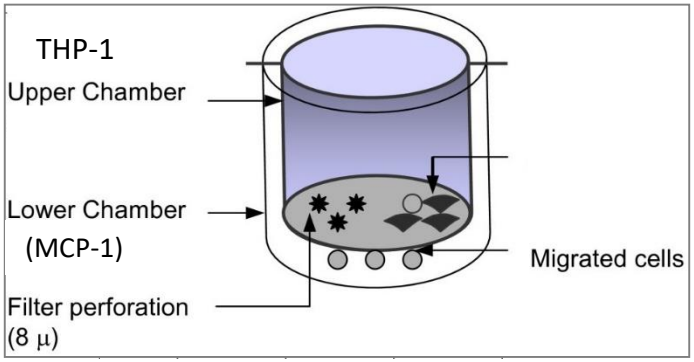
LP Chuang et al. *Plos One.* 2014;9(11):e113304.

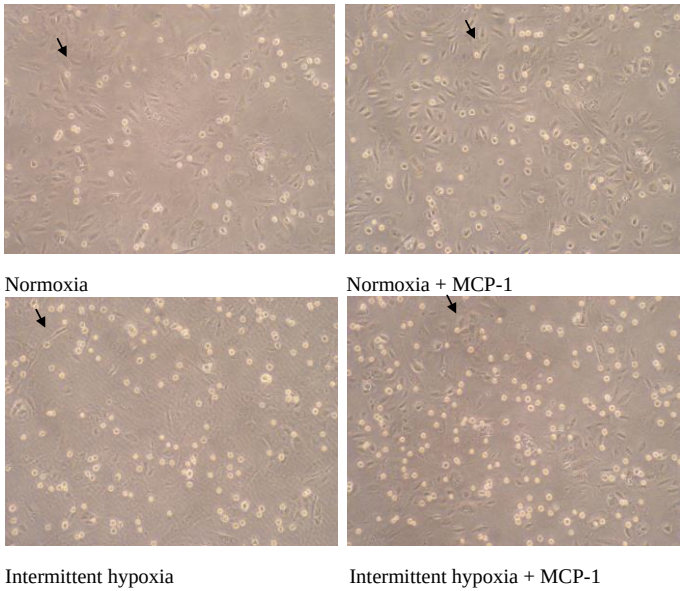
IH ↑ migration toward MCP-1 & adhesion to HUVEC in THP-1 cells

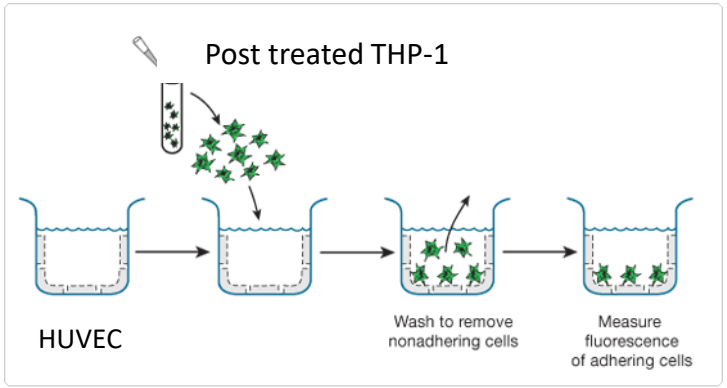
(A)



Normoxia Intermittent hypoxia

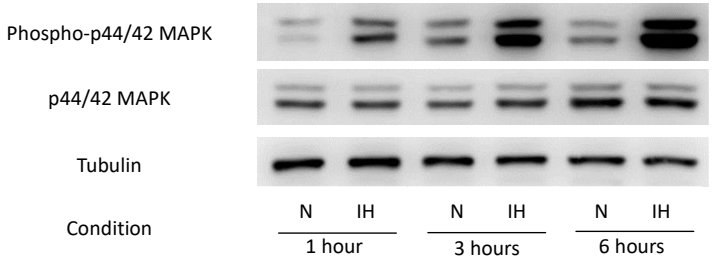






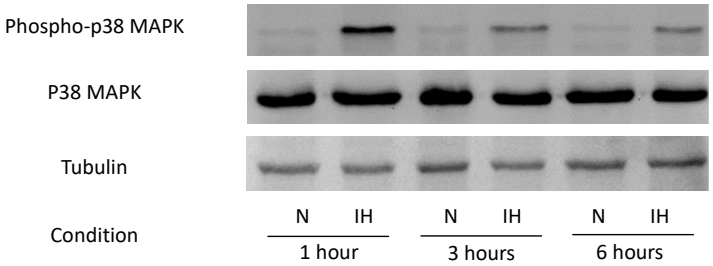
LP Chuang et al. *Plos One.* 2014;9(11):e113304.

Possible involved pathway and Human data

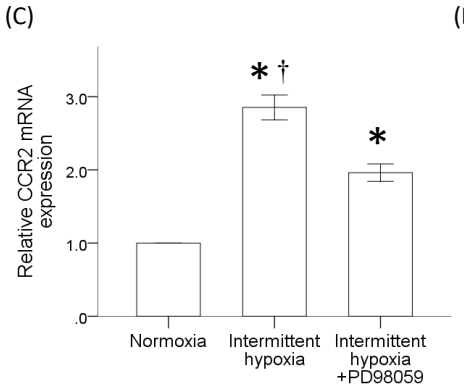


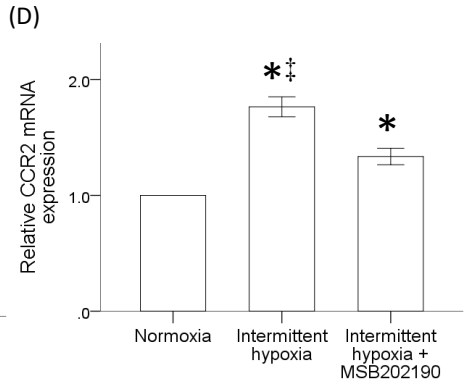
(N: normoxia; IH: intermittent hypoxia)

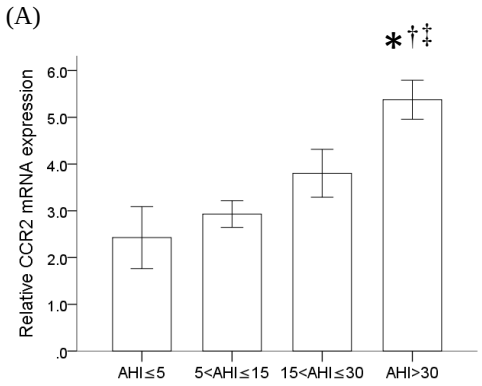
(B)

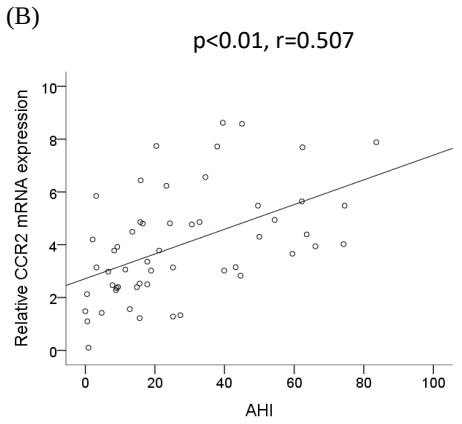


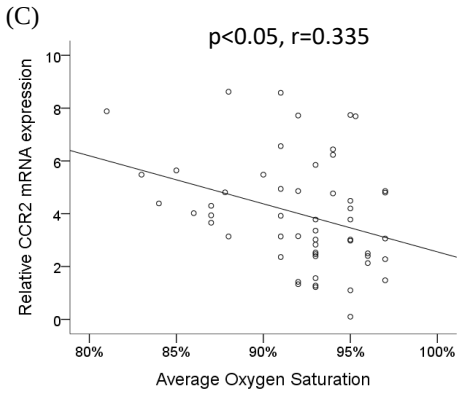
(N: normoxia; IH: intermittent hypoxia)

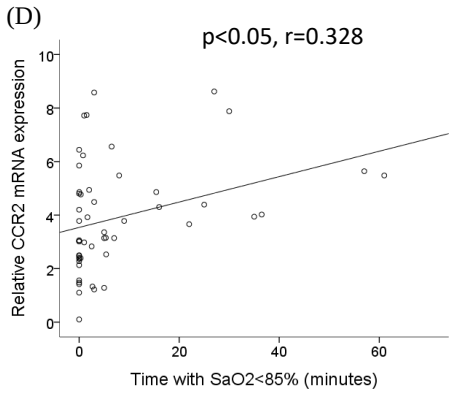






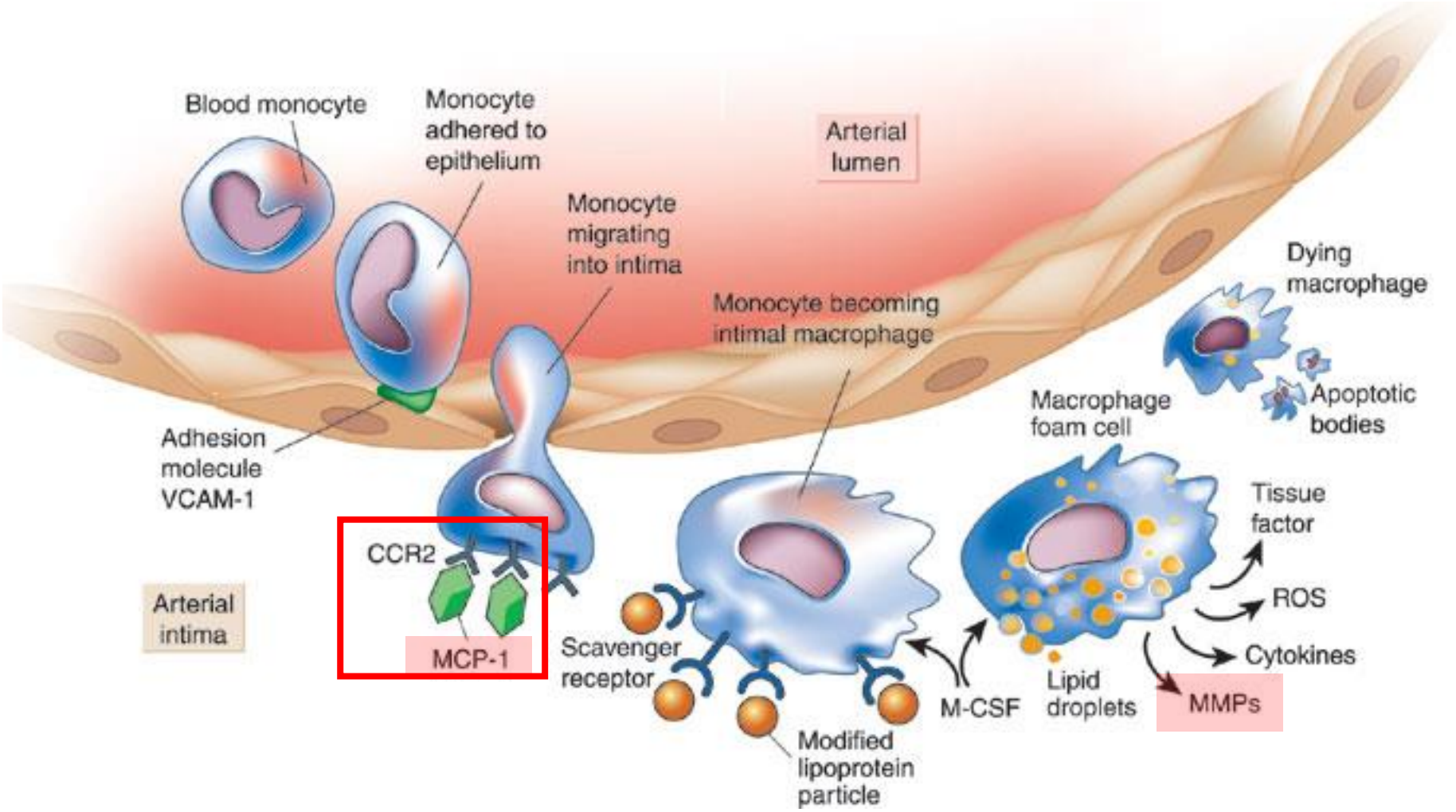






LP Chuang et al. *Plos One.* 2014;9(11):e113304.

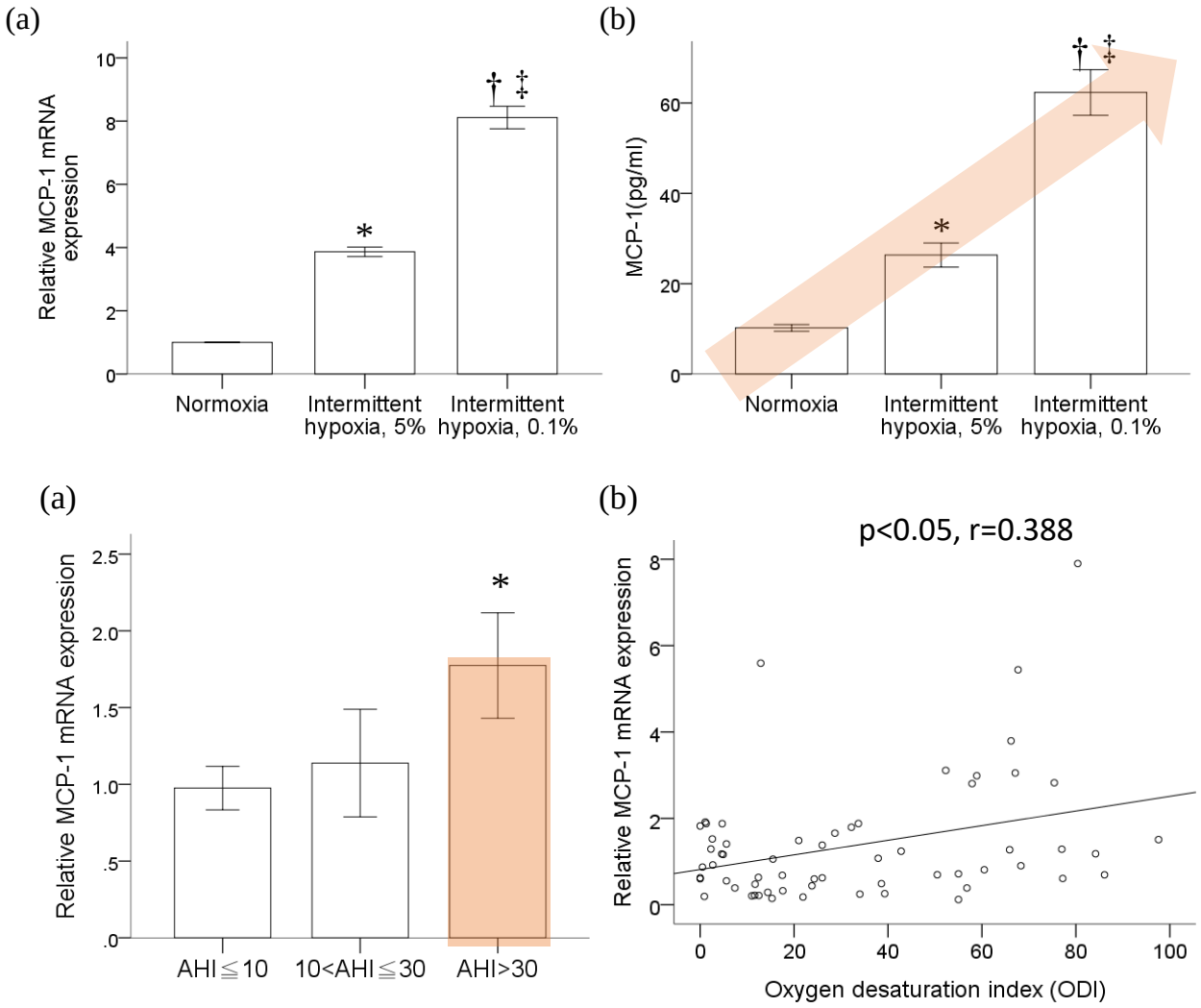
Monocytes, Endothelium, Inflammation and Atherosclerosis



Circulation. 1993 Aug;88(2):358-63.

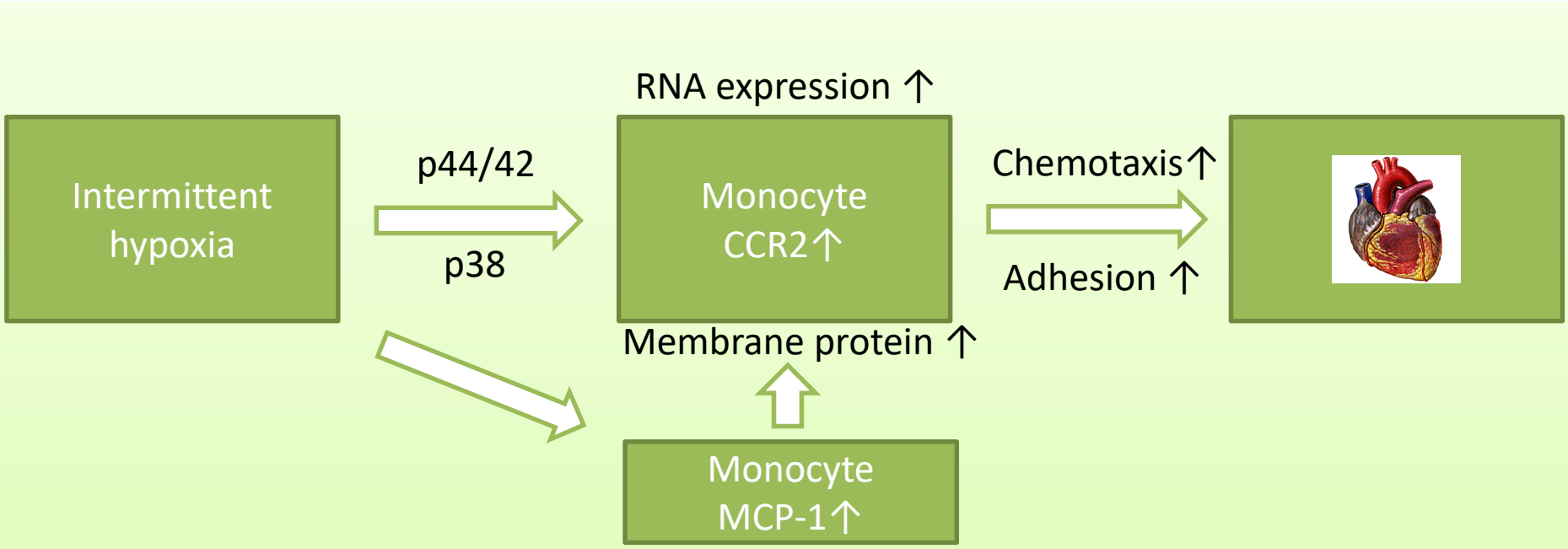
Nature. 2002 Dec;420:868-874.

IH ↑ monocyte MCP-1 expression & ↑ monocyte MCP-1 expression from severe OSA patients



LP Chuang et al. *Sleep Breath. 2016 Mar;20(1):425-33.*

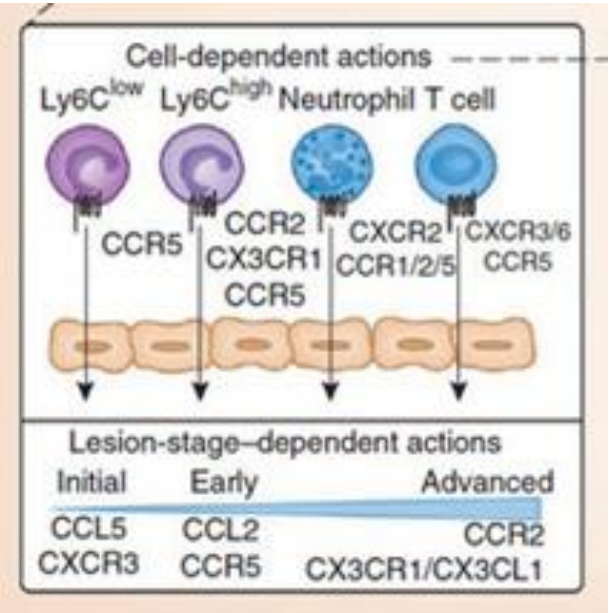
Intermittent Hypoxia Active Chemotaxis in Monocytes of OSA patients



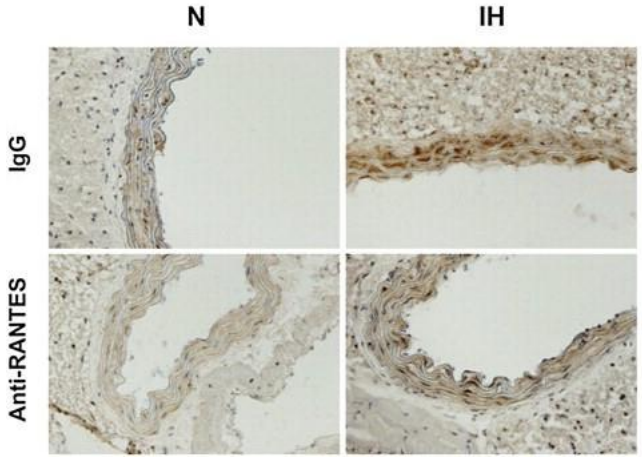
Monocyte CCR2, MCP-1 mRNA expression ↑ in OSA

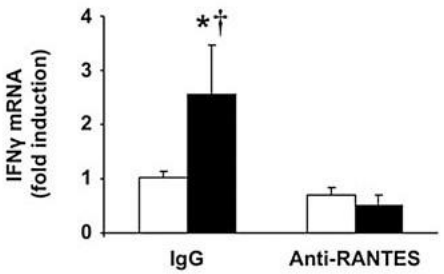
LP Chuang et al. *Plos One*. 2014;9(11):e113304.
LP Chuang et al. *Sleep Breath*. 2016 Mar;20(1):425-33.

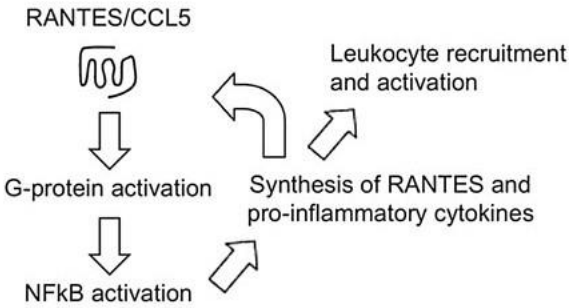
Chemokines & Receptor



Ligands	Receptors
Monocyte chemoattractant protein-1 **(MCP-1)**	Chemokine (C-C motif) receptor 2 **(CCR2)**
Regulated and normal T cell expressed and secreted **(RANTES)**	Chemokine (C-C motif) receptor 5 **(CCR5)**
Chemokine (C-X3-C motif) ligand 1 **(Fractalkine)**	CX3C chemokine receptor 1 **(CX3CR1)**





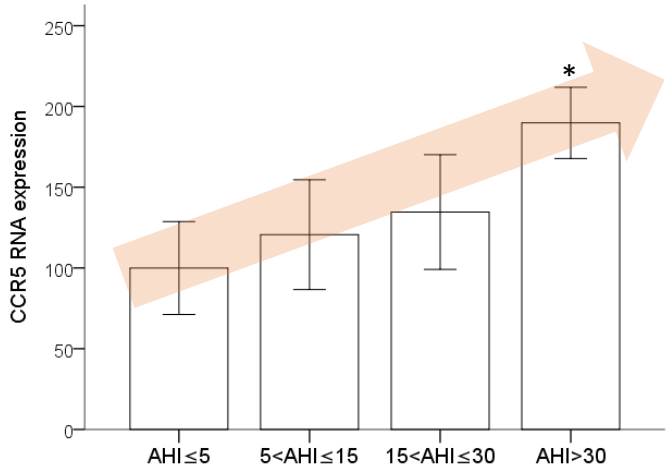


Respiration. 2004 Nov-Dec;71(6):580-6.

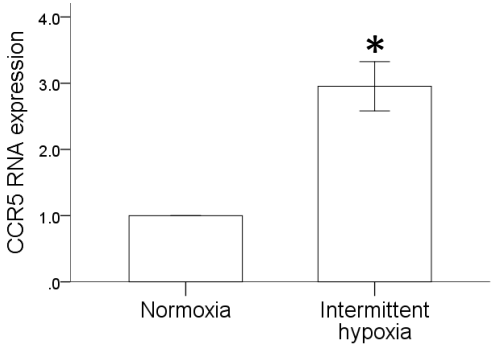
Am J Respir Crit Care Med. 2011 Sep 15;184(6):724-31.

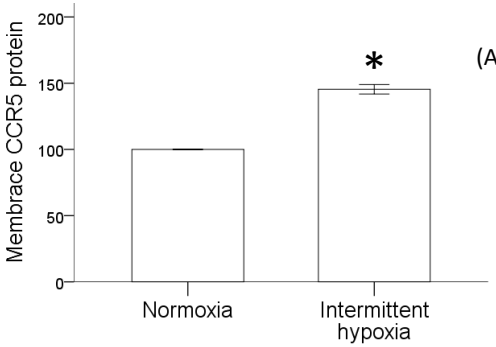
Eur Respir J. 2011 Jan;37(1):119-28.

↑ monocyte CCR5 expression from severe OSA patients & under IH



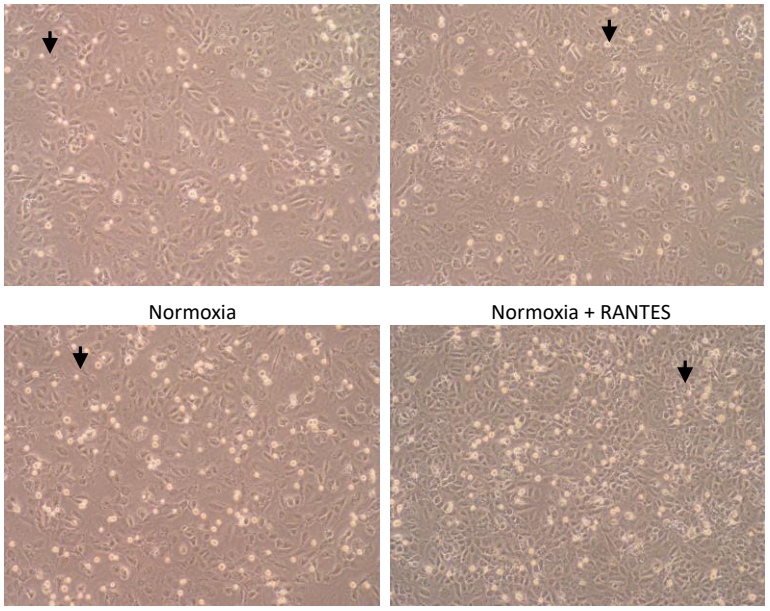
(mean ± SE, *: P<0.05 vs. AHI≤5)



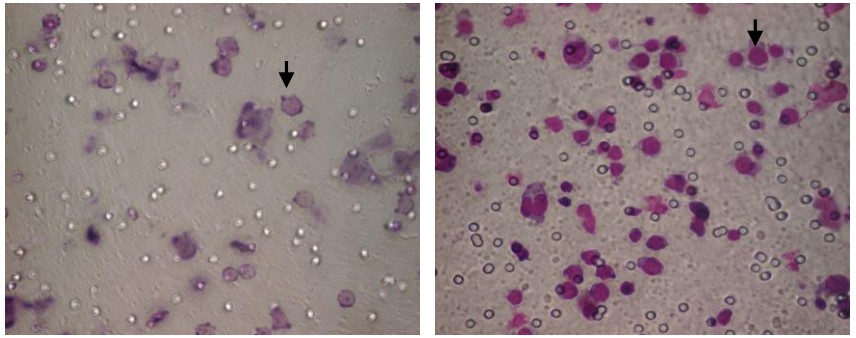


(mean ± SE, *: P<0.05 vs. Normoxia)

(A)

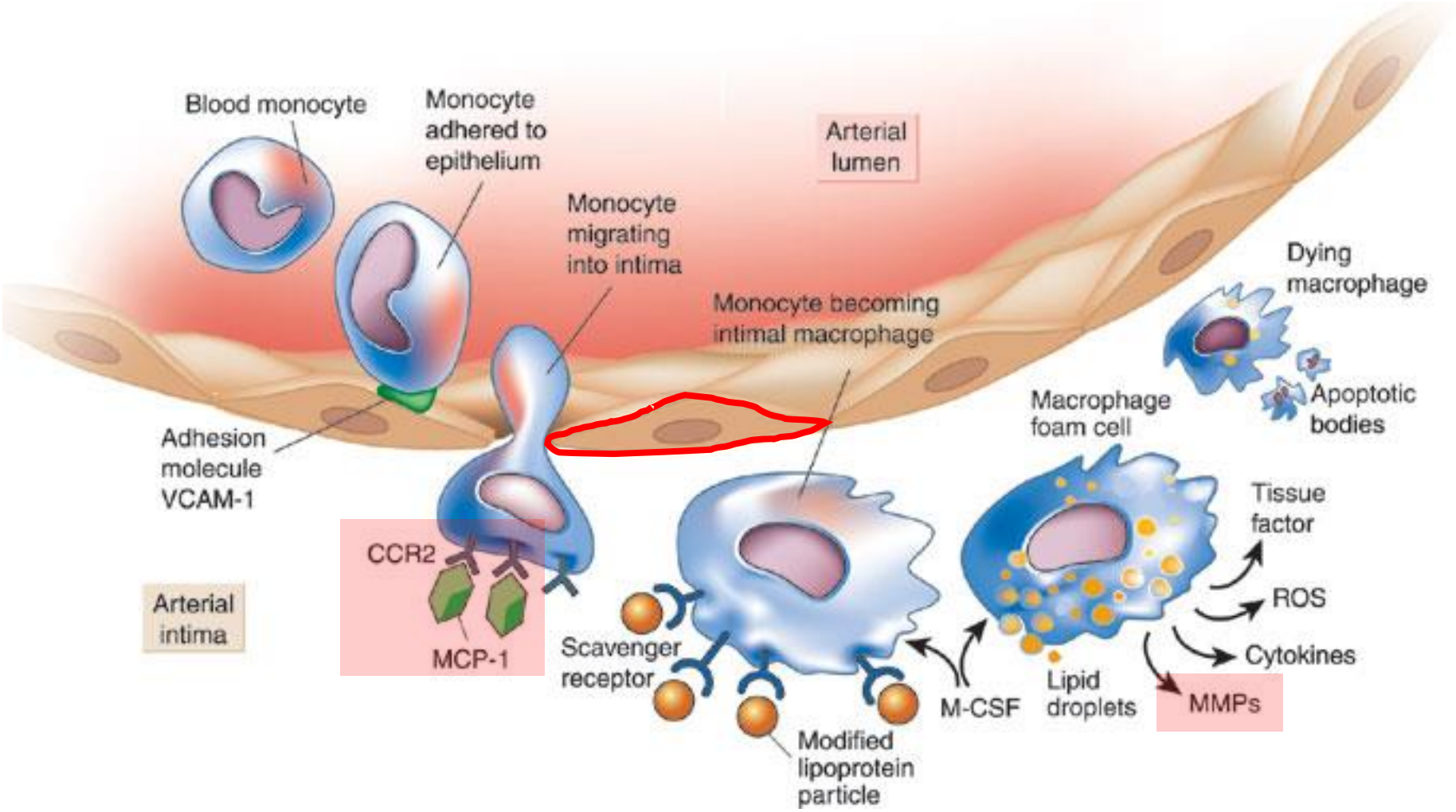


(A)



LP Chuang et al. *Sleep Breath*. 2019 Dec;23(4):1177-1186.

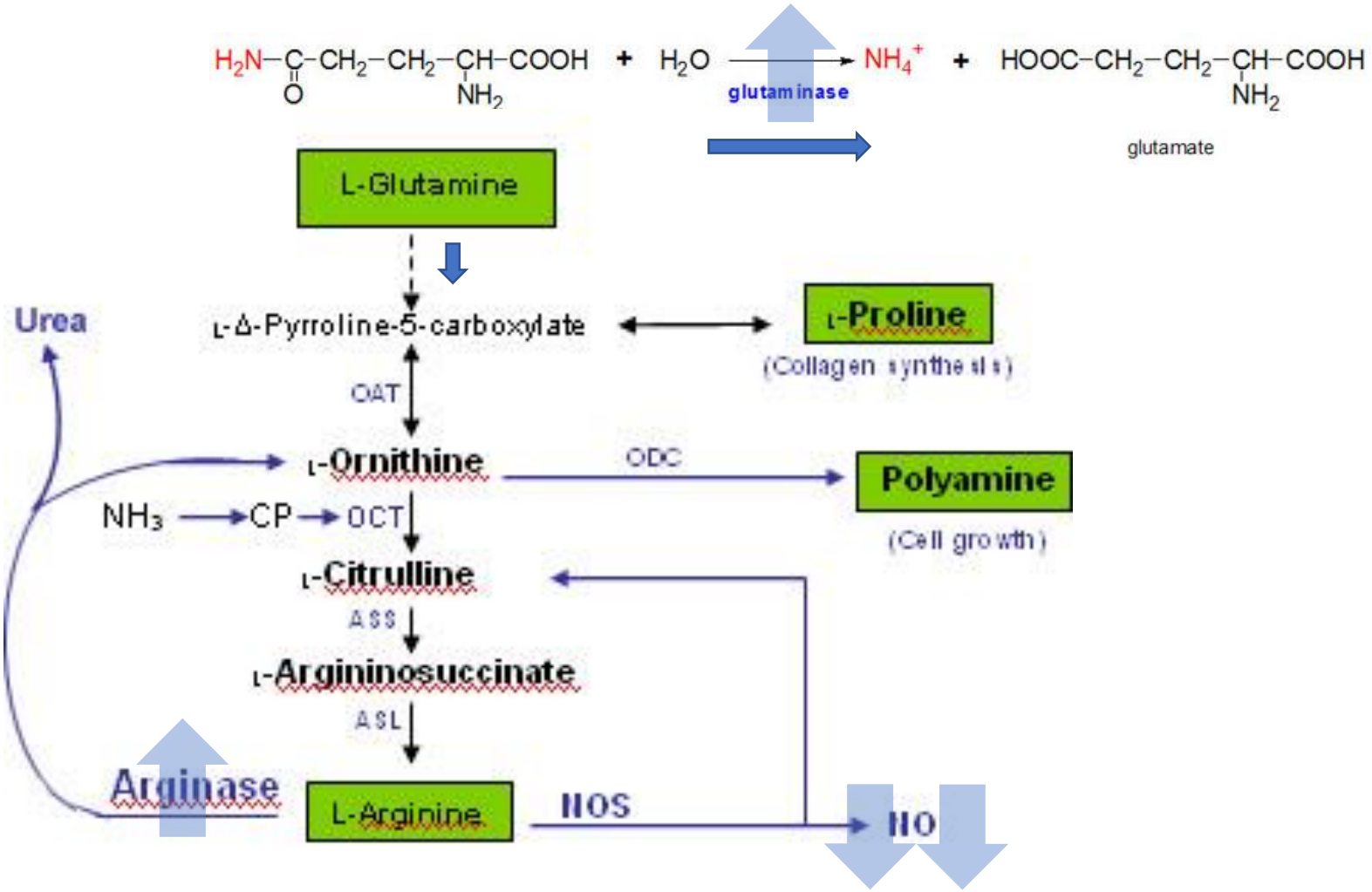
Monocytes, Endothelium, Inflammation and Atherosclerosis



Circulation. 1993 Aug;88(2):358-63.

Nature. 2002 Dec;420:868-874.

Role of arginase & glutaminase in vascular endothelial dysfunction



Adapted from: *CNS Drugs*. 2007;21(11):885-900

Circulating nitric oxide is suppressed in OSA and is reversed by nasal CPAP

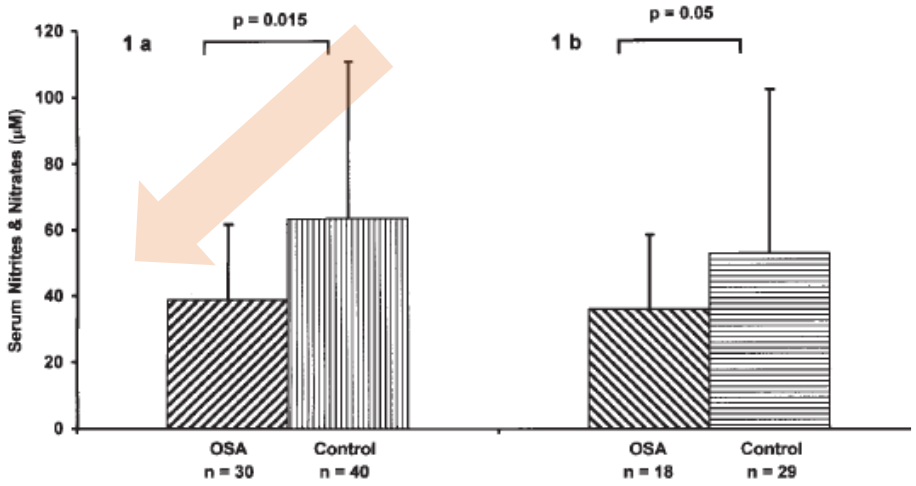


Figure 1. (*a*) Serum nitrite/nitrate levels in OSA subjects (n = 30) and control subjects (n = 40). (*b*) Serum nitrite/nitrate levels in BMI-matched OSA subjects (n = 18) and control subjects (n = 29).

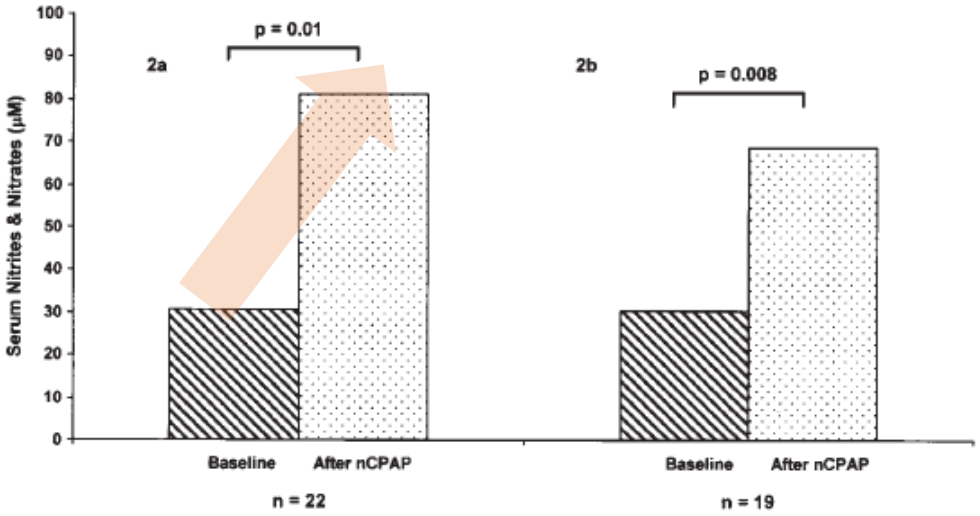
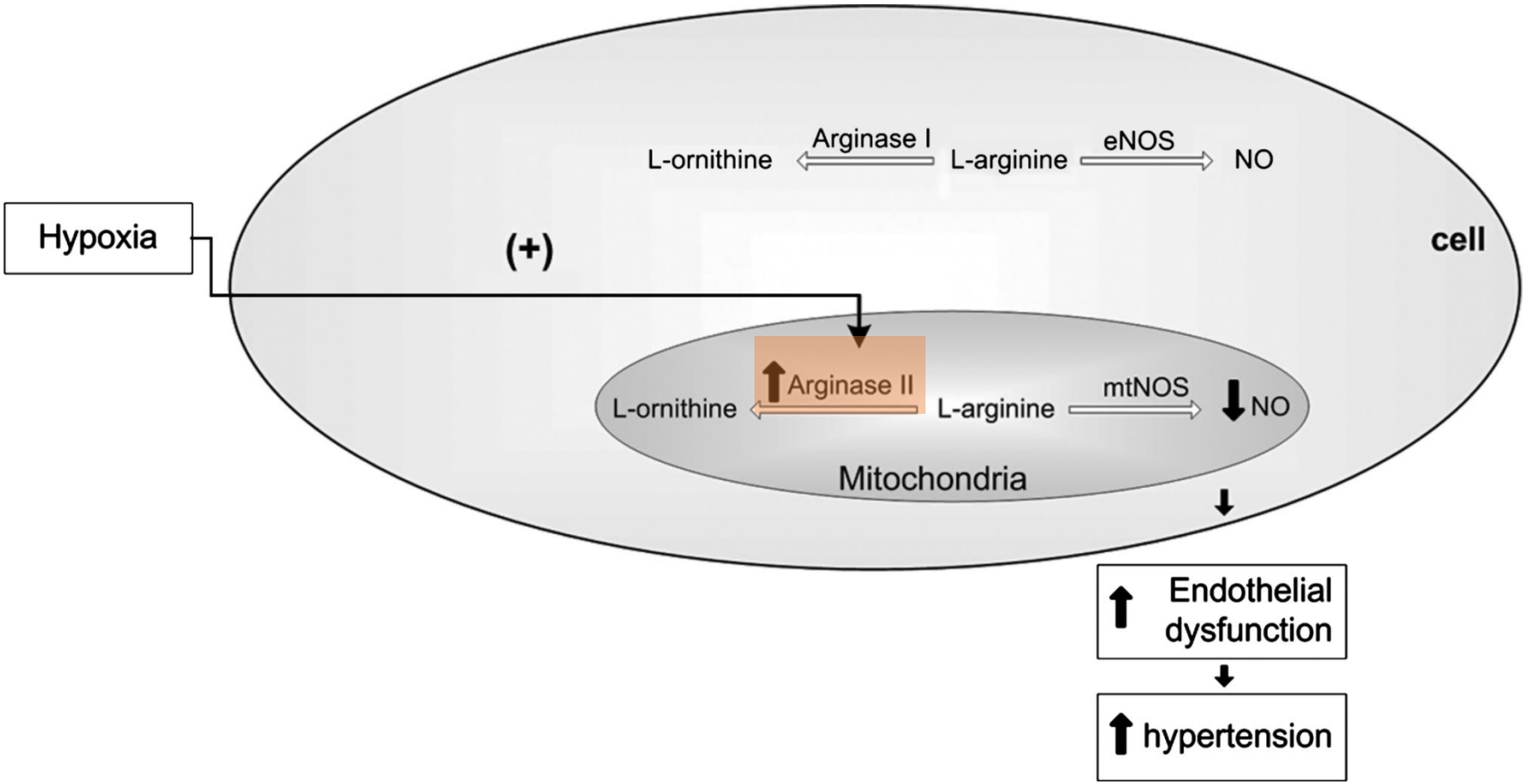


Figure 2. (*a*) Serum nitrite/nitrate levels in OSA subjects at baseline and after nCPAP (n = 22). (*b*) Serum nitrite/nitrate levels in OSA subjects, excluding three subjects on antihypertensive mediations, at baseline and after nCPAP (n = 19).

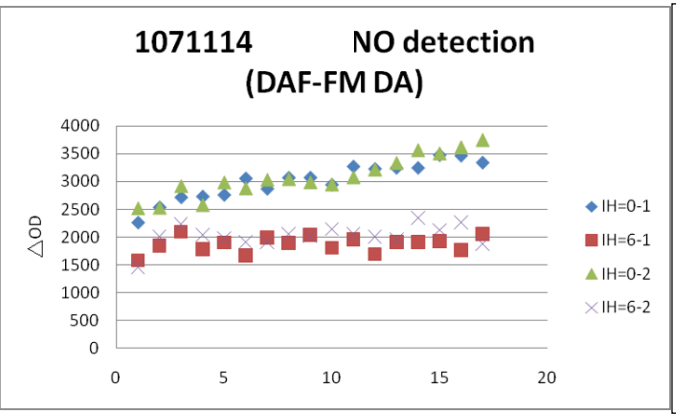
Am J Respir Crit Care Med. 2000 Dec;162(6):2166-71.

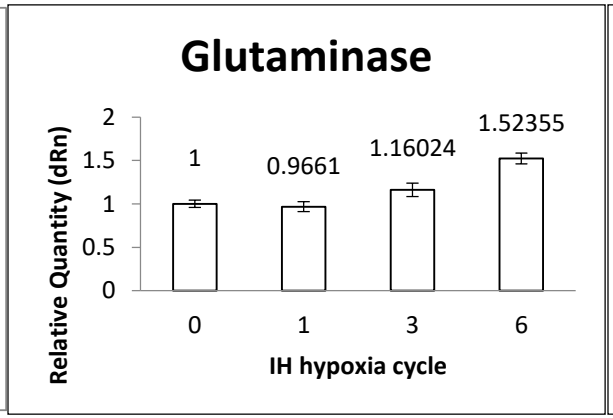
↑Arginase Expression and Activity in Hypertensive Rats Exposed to Intermittent Hypobaric Hypoxia

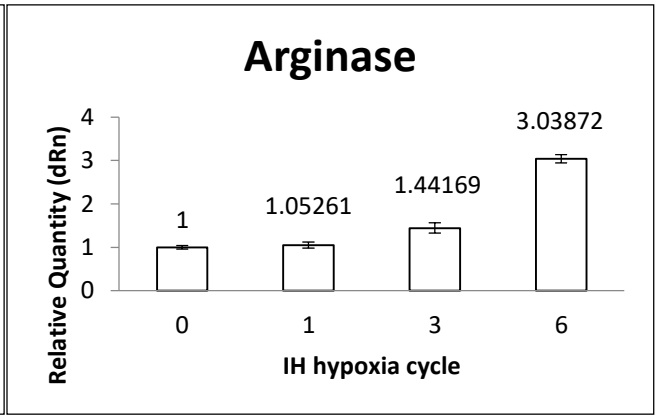


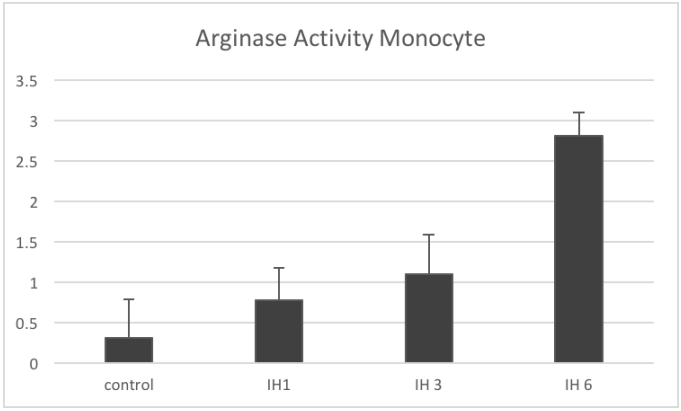
High Altitude Med Bio 2009; 10,4, 373-381

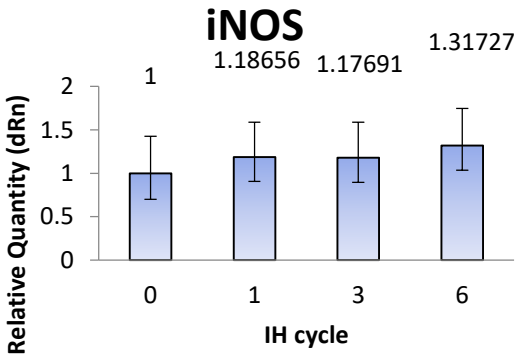
↓NO in endothelial cells via intermittent hypoxia through ↑Arginase and Glutaminase

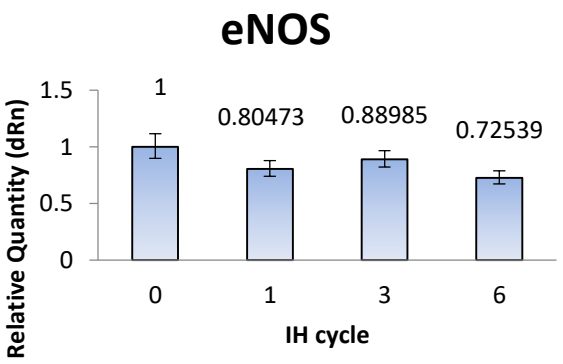












Data in preparation…

Outline

- Endothelium damage in obstructive sleep apnea
- Biomarkers of endothelium damage
  - Cardiovascular
  - Renal

High prevalence of CKD in OSA

- The prevalence of CKD(GFR<60) was found to be higher(30.5%) across all individuals diagnosed with 1624 OSA (9.1% in comparison)

Hypertens Res 2008; 31: 249–255

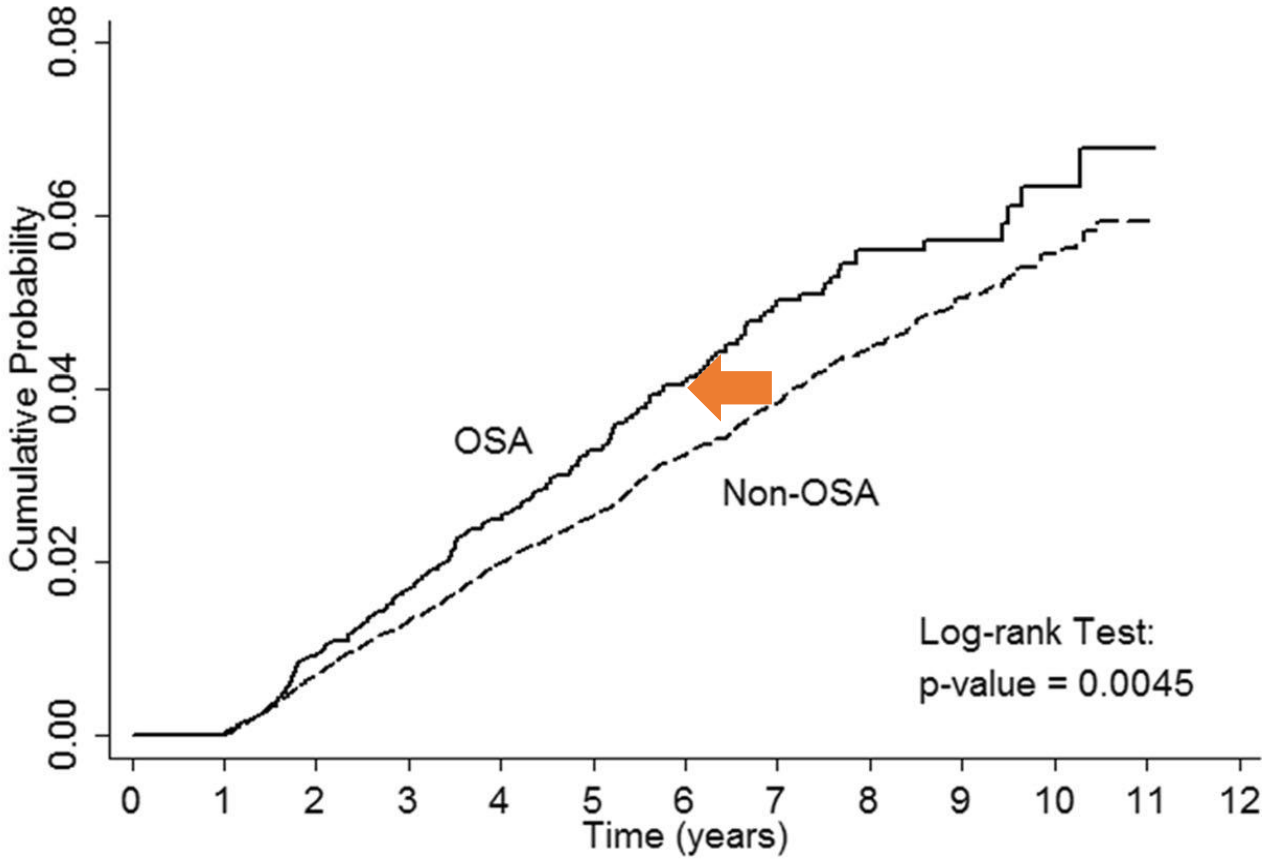
- The prevalence of stage 1 + stage 2 CKD(GFR<60) in non-HTN, non-DM OSA patient in Taiwan = 18% (general population = 6.5%)

Lancet 2008; 371: 2173–2182
Nephrol Dial Transplant (2011) 0: 1–6

- Associations have been found between the apnea hypopnea index (AHI) and the UACR (urine albumin-to-creatinine ratio)

Sleep 2007;30: 923–929
Am J Kidney Dis 2008; 52:285–293

Simple OSA without HTN or DM accelerate kidney dysfunction: a population follow-up cohort study from Taiwan



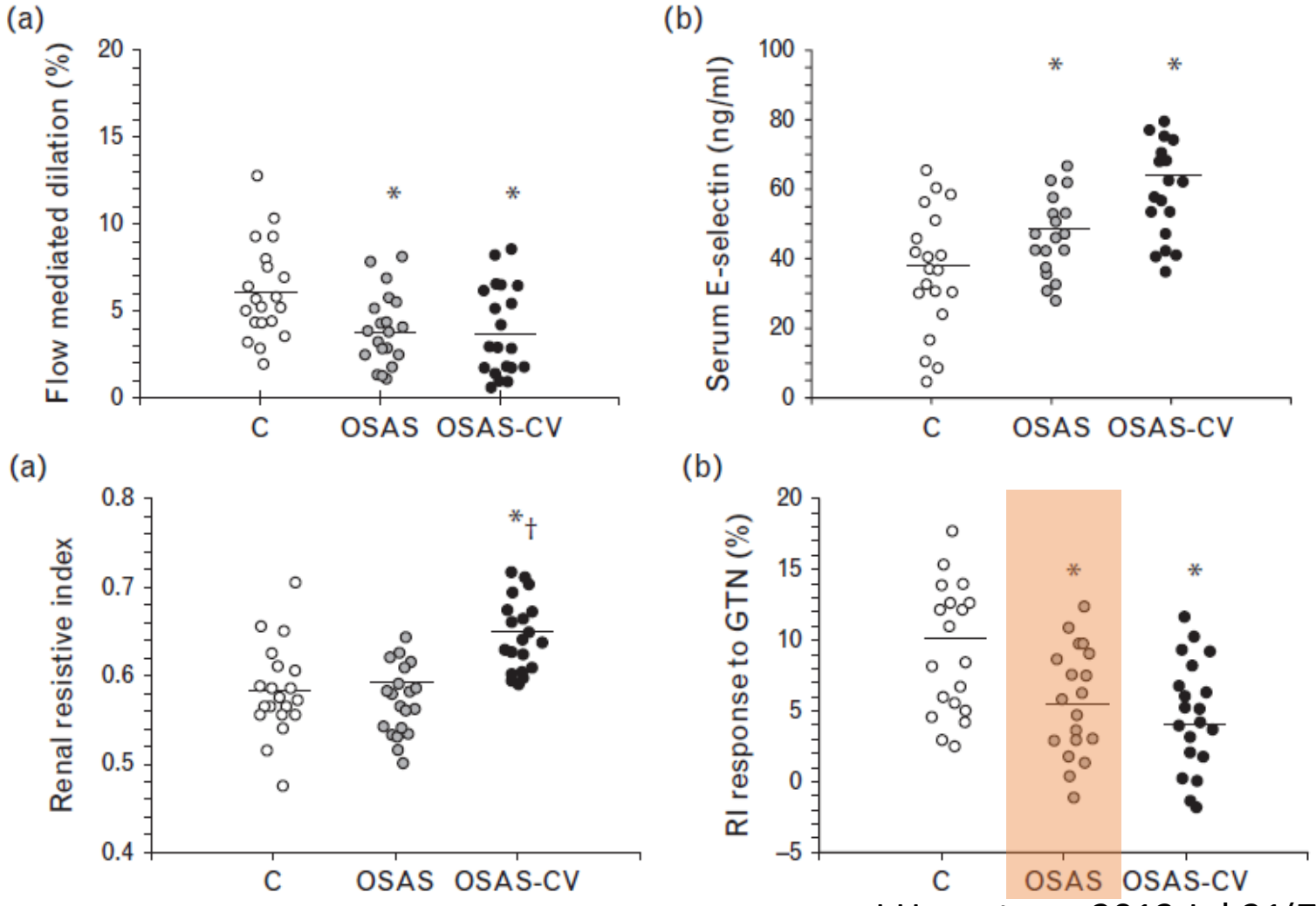
Number at risk

Non-OSA	34330	23663	14611	7943	3248	168
OSA	6866	4733	2917	1582	655	34

- The median duration until development of CKD in the OSA cohort was 3.2 years
- 2.5 months earlier than that in the non-OSA cohort

Lin YS, et al. *Sleep Breath*. 2017 Mar;21(1):85-91

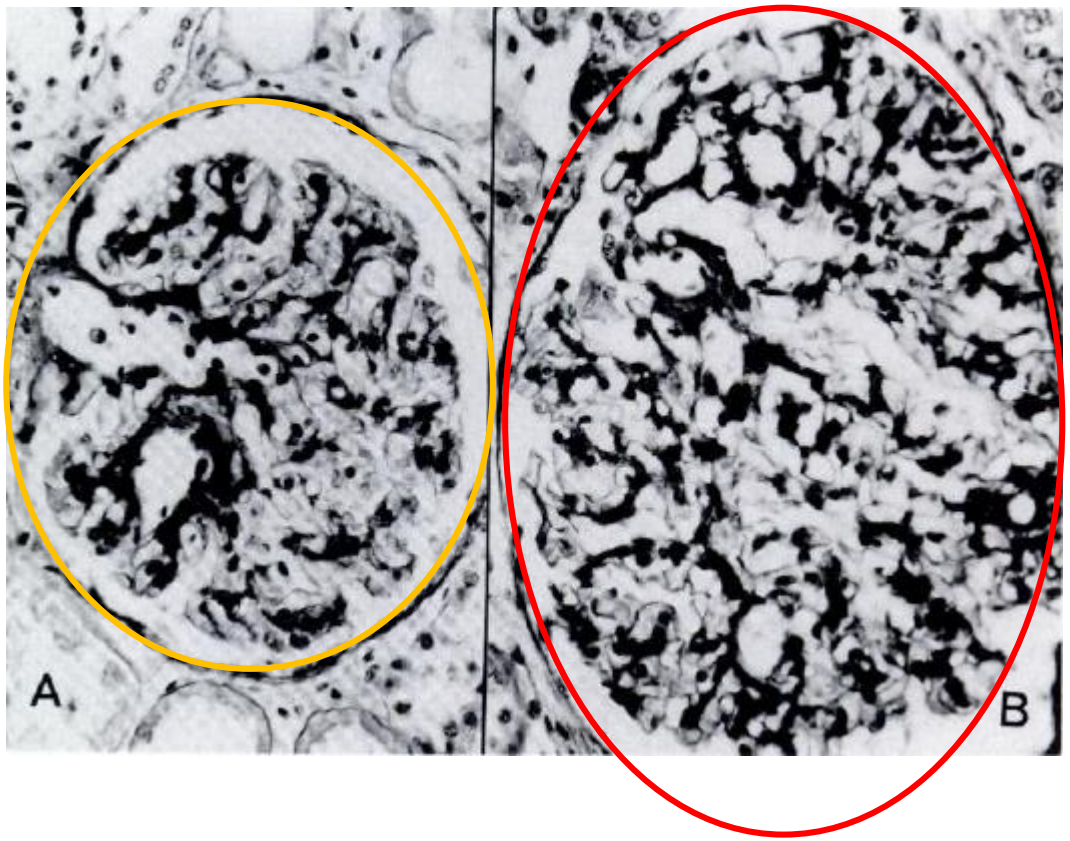
Renal vasodilating capacity and endothelial function are impaired in patients with OSA



J Hypertens. 2013 Jul;31(7):1456-64.

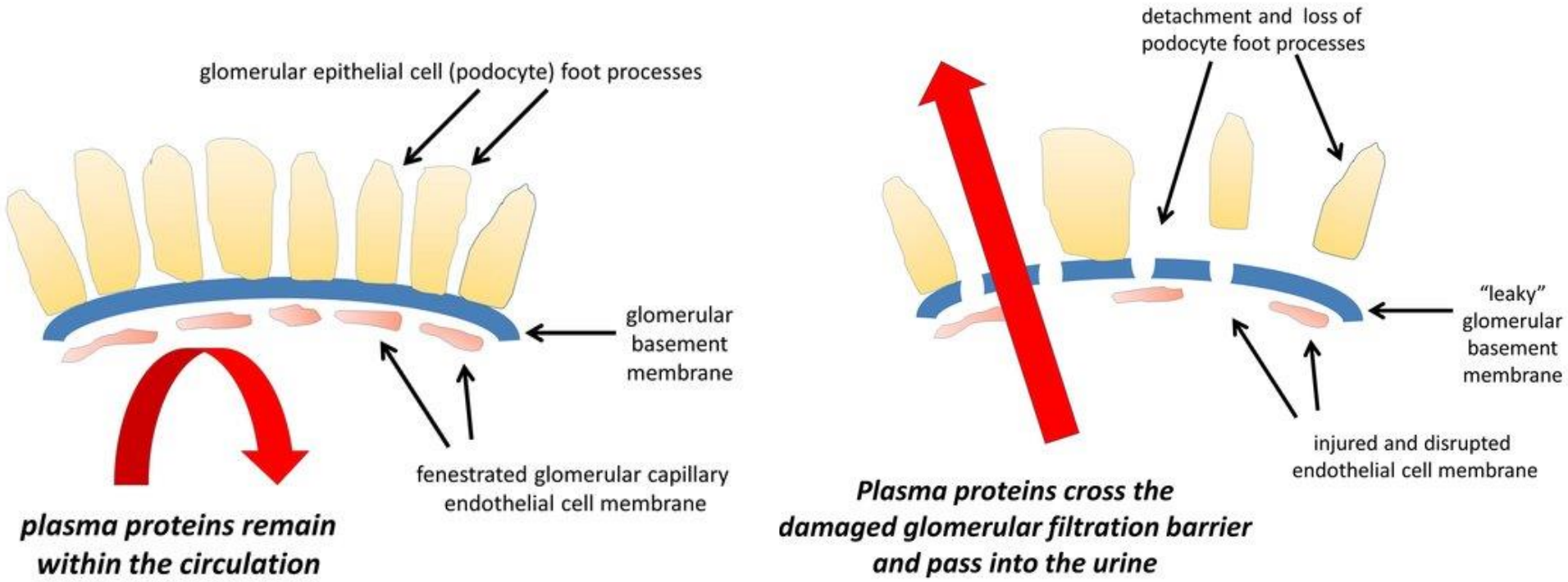
OSA increase glomerular filtration

- Renal biopsies of OSA patients: glomerulomegaly and focal segmental sclerosis ➔ may result from increased glomerular filtration.



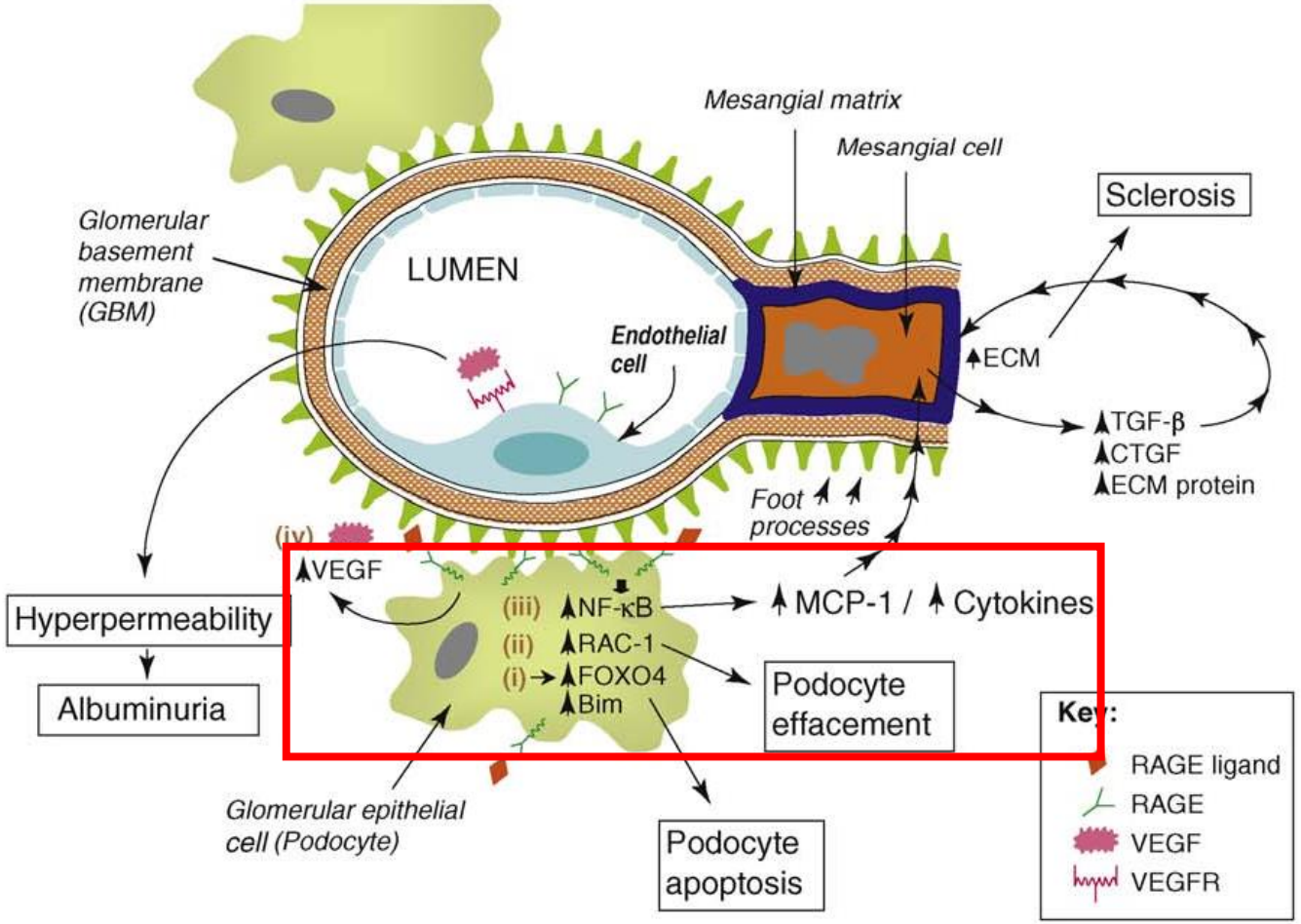
Am J Kidney Dis 1987; 10: 470-2

Diagnosis and management of nephrotic syndrome



The Practitioner 2017; 261(1801):11-15

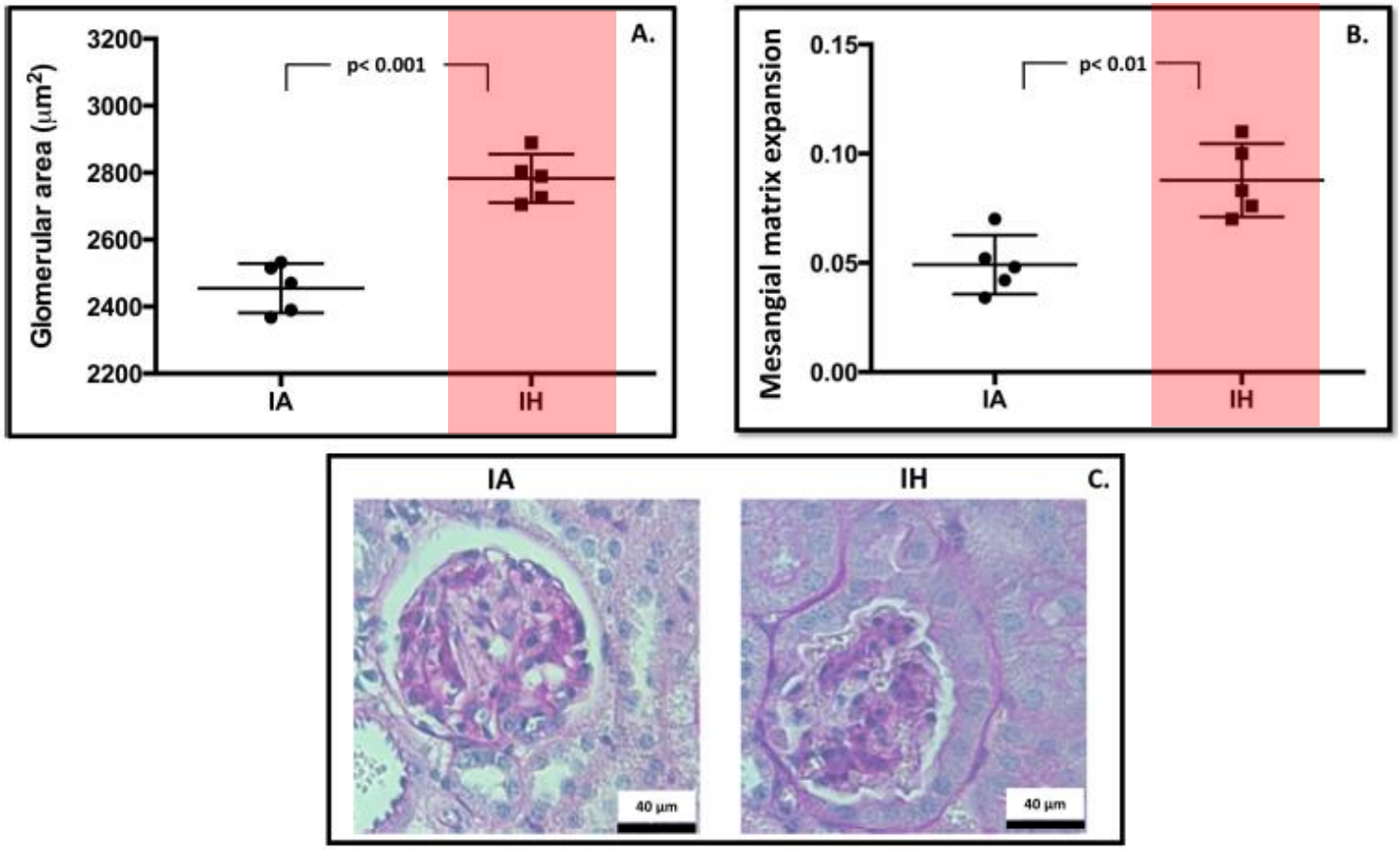
Glomerulosclerosis and proteinuria: Roles in podocytes and endothelial cells



Trends Endocrinol Metab. 2010 Jan;21(1):50-6.

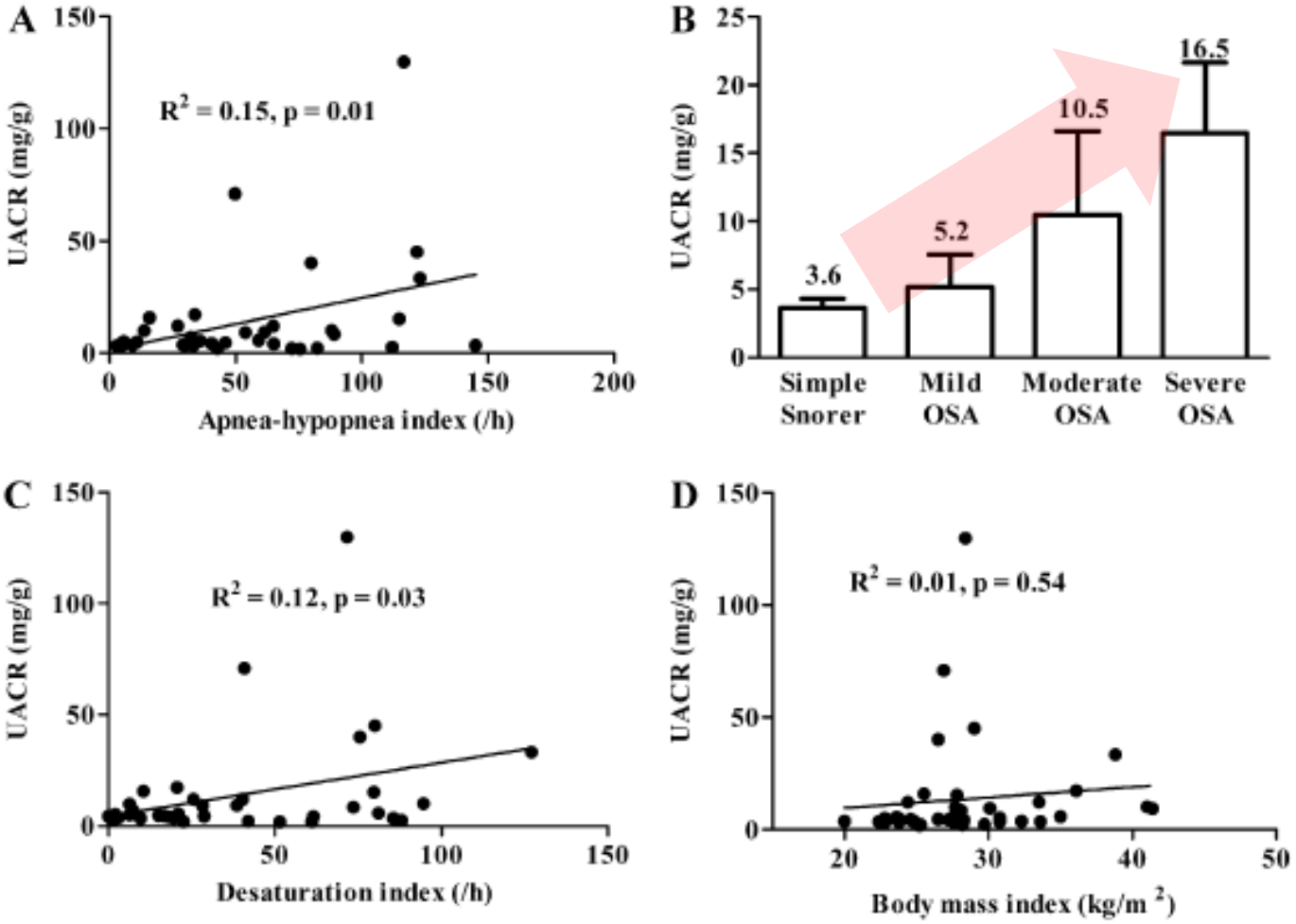
Intermittent hypoxia causes histological kidney damage and increases growth factor expression in a mouse model of OSA

- Intermittent hypoxia, 60days, B6 mice



PLoS One. 2018 Feb 1;13(2):e0192084.

Obstructive sleep apnea: a stand-alone risk factor for chronic kidney disease

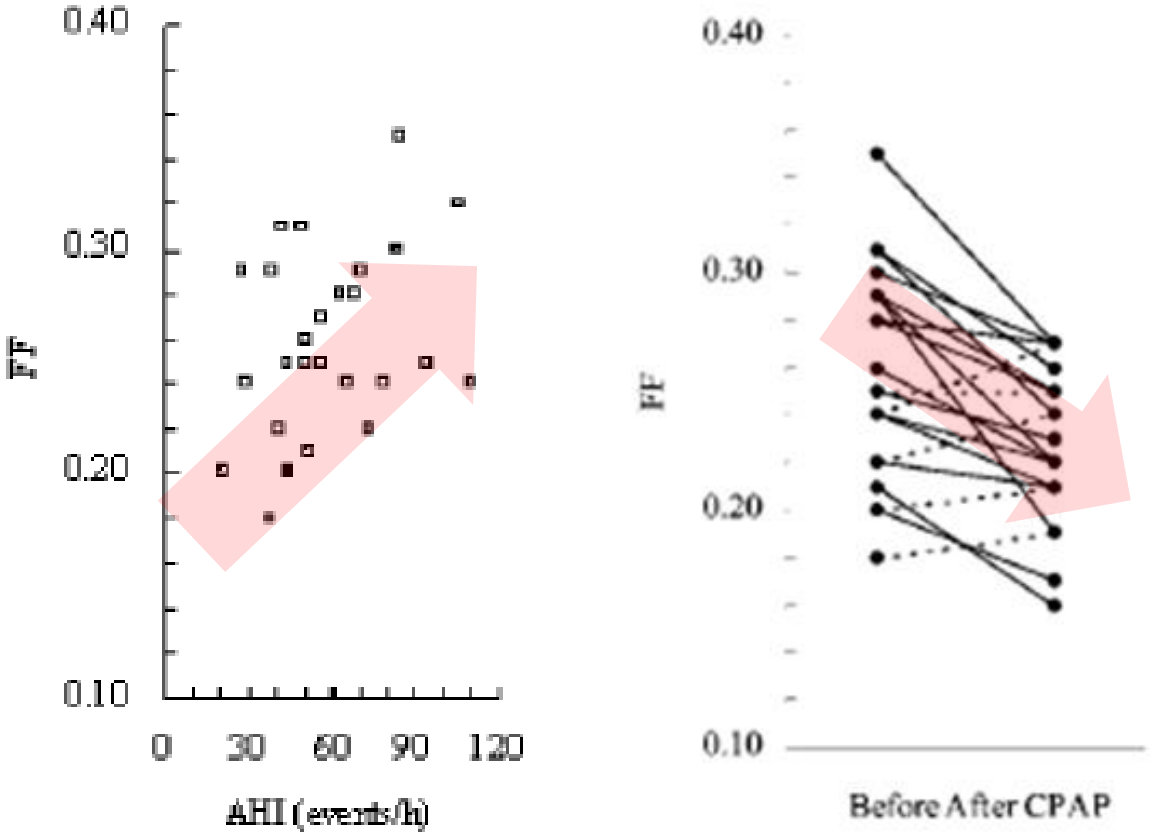


- 40 suspect OSA patients in Taiwan (CGMH Linko & Chiayi)
- Free of HTN, DM or other systemic disease

Chou YT, et al. *Nephrol Dial Transplant* 2011 Jul;26(7):2244-50.

Glomerular hyperfiltration improving after cPAP

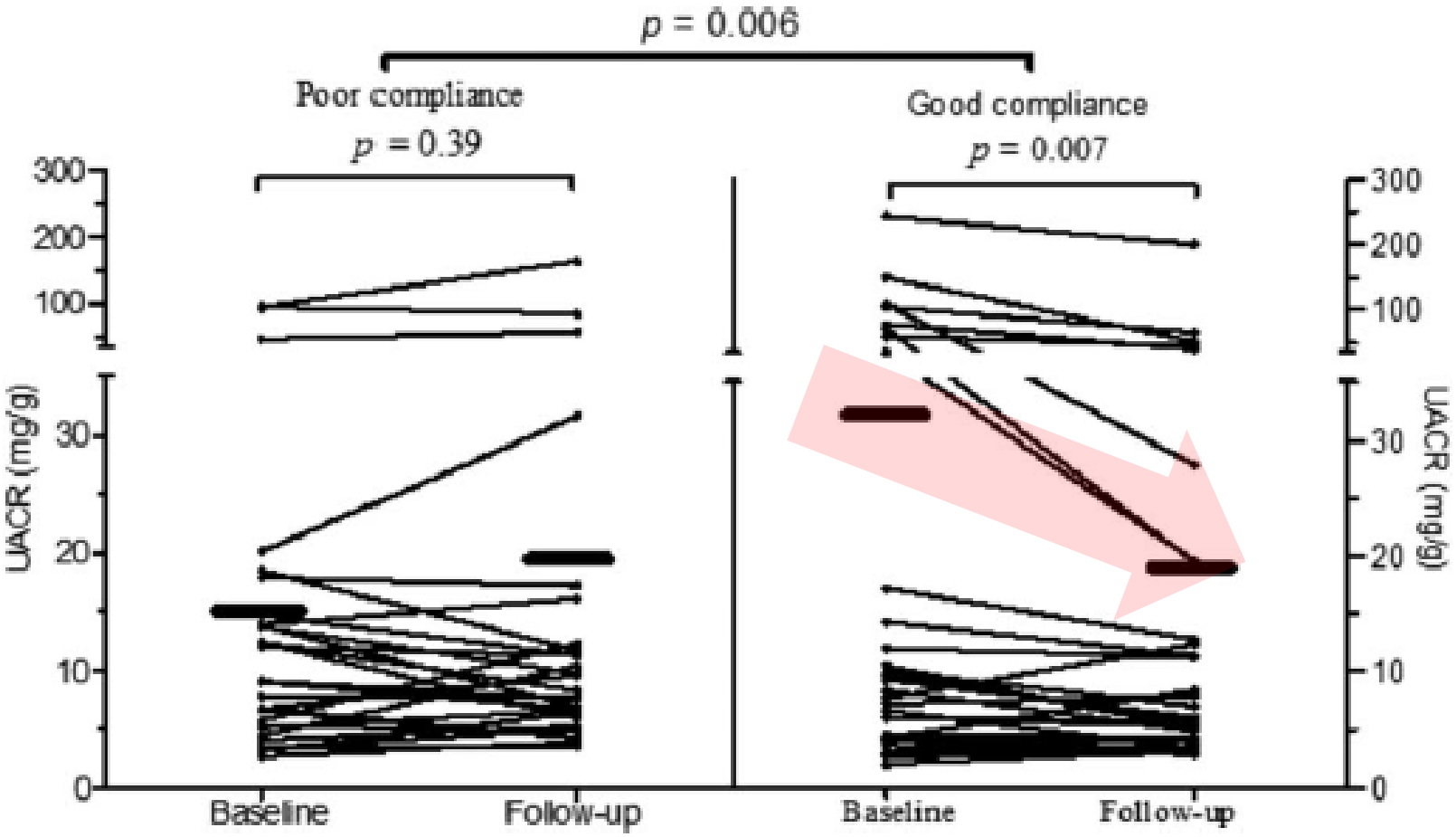
- 27 OSA, before cPAP, filtration fraction (FF) ↑ with AHI ↑;
- cPAP for one week, FF↓



Clin Sci 2004; 107: 317–322

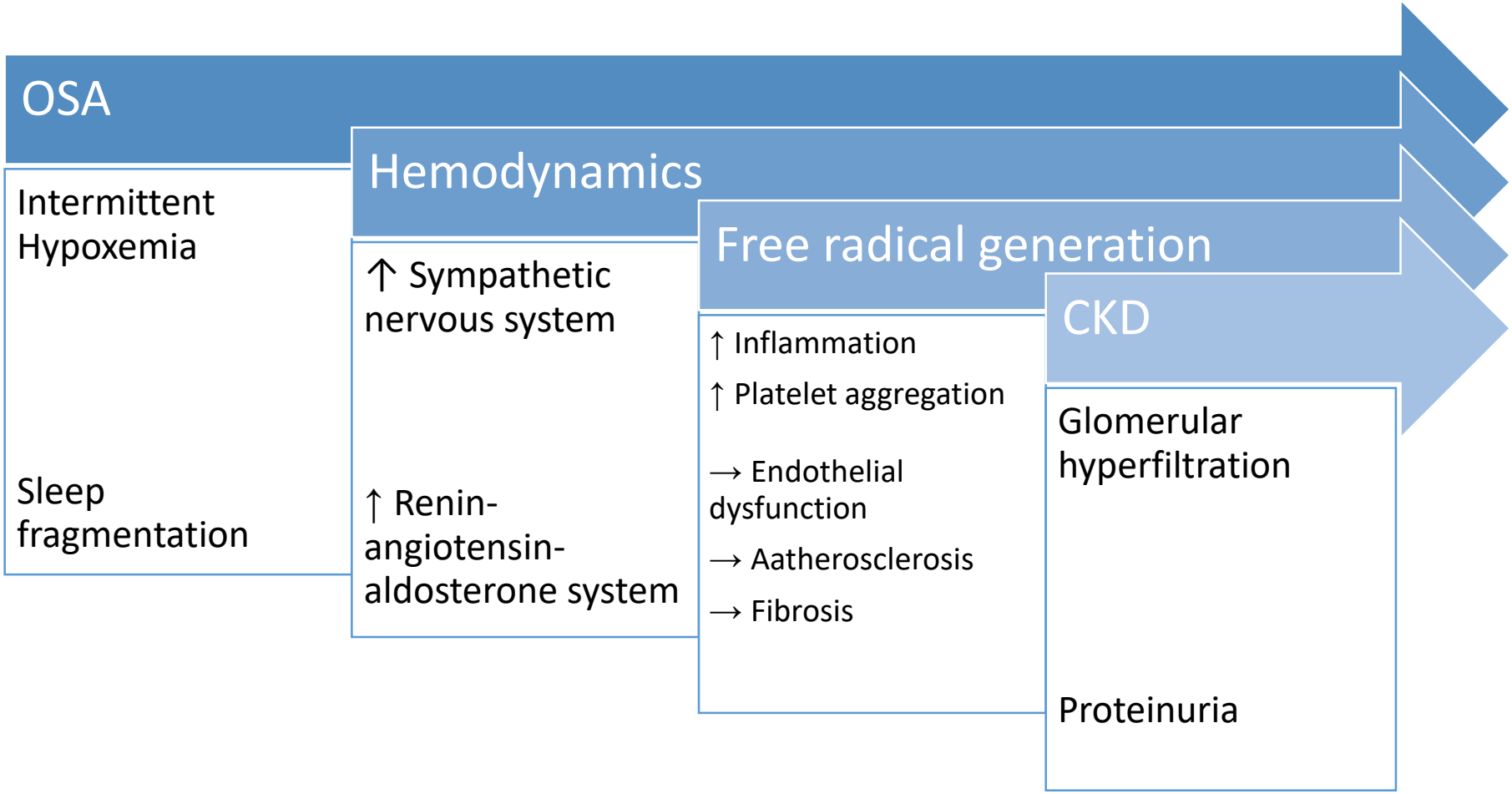
Reversibility of albuminuria and CPAP compliance in patients of OSA

68 OSA; 6 months CPAP

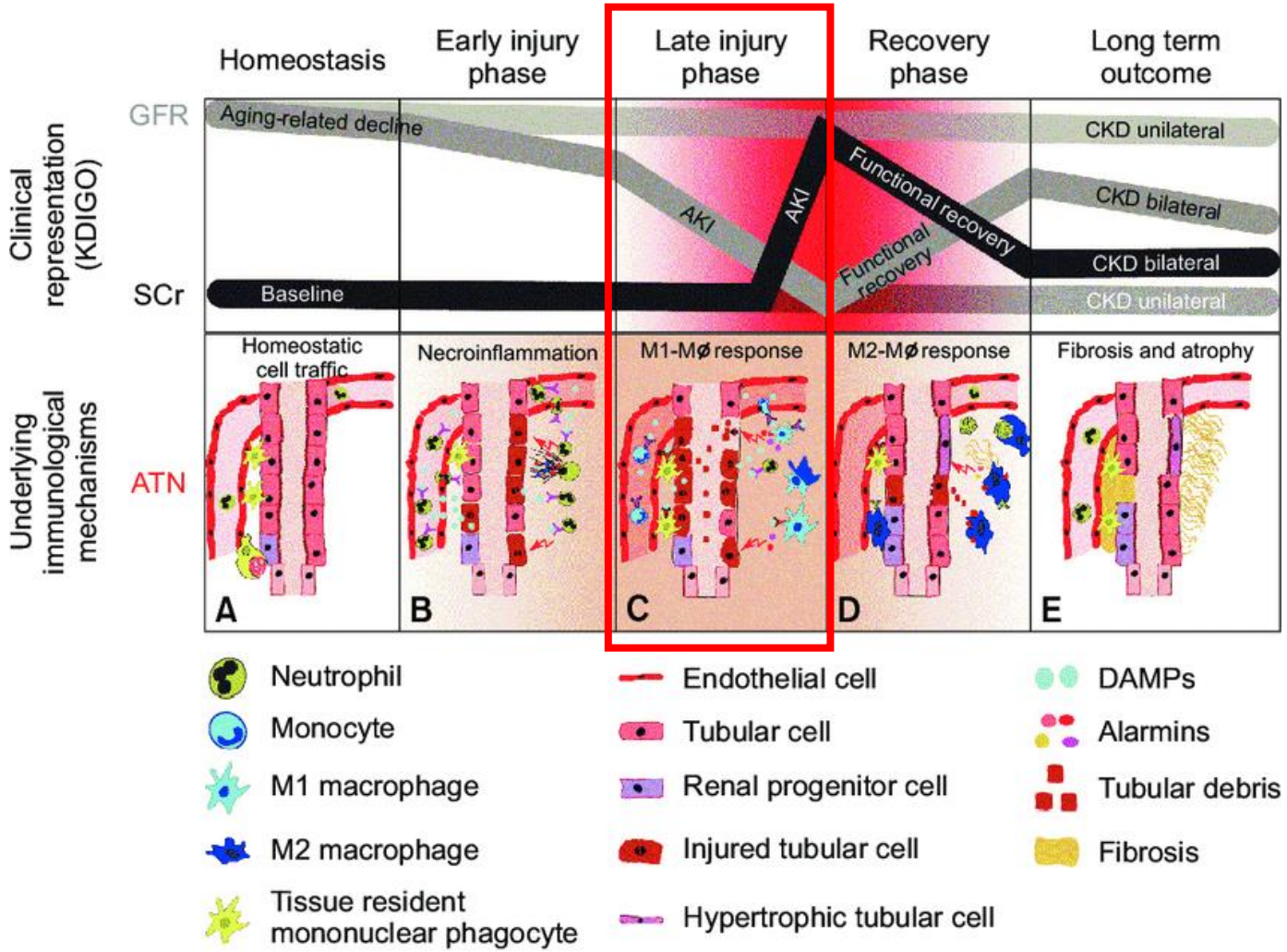


Chen NH, et al. *Medicine (Baltimore)*. 2016 Jun;95(26):e4045.

OSA contribute renal function impairment: pathophysiology

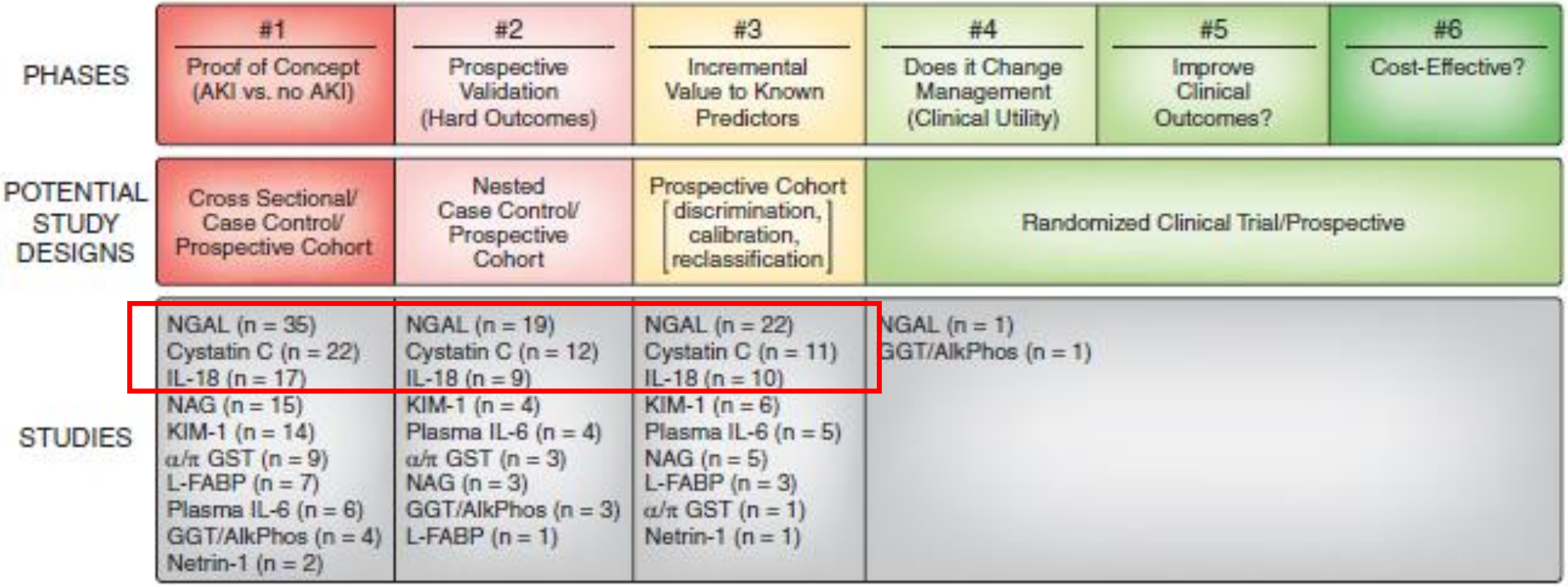


Immune mechanisms in the different phases of acute tubular necrosis



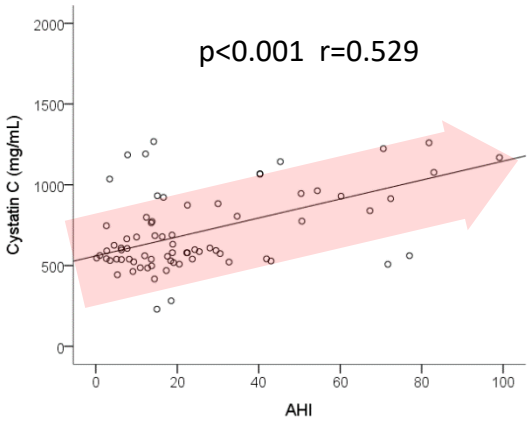
Kidney Res Clin Pract. 2018 Sep;37(3):185-196.

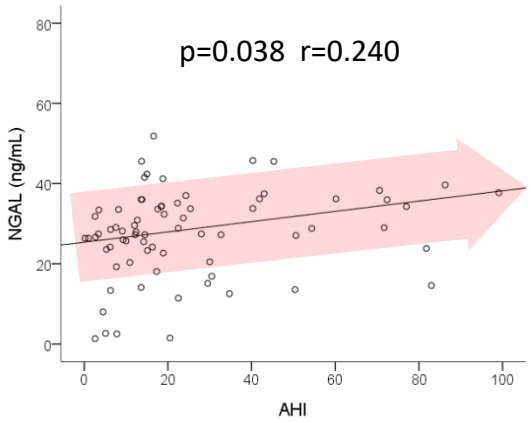
Biological Markers of Acute Kidney Injury



J Am Soc Nephrol 22: 810–820, 2011

Elevated Serum Markers of Acute Kidney Injury in Patients with OSA





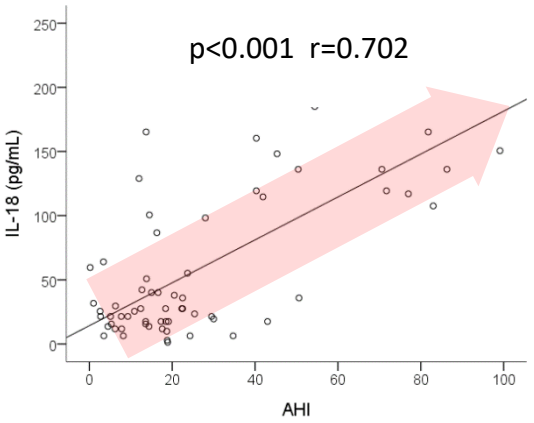


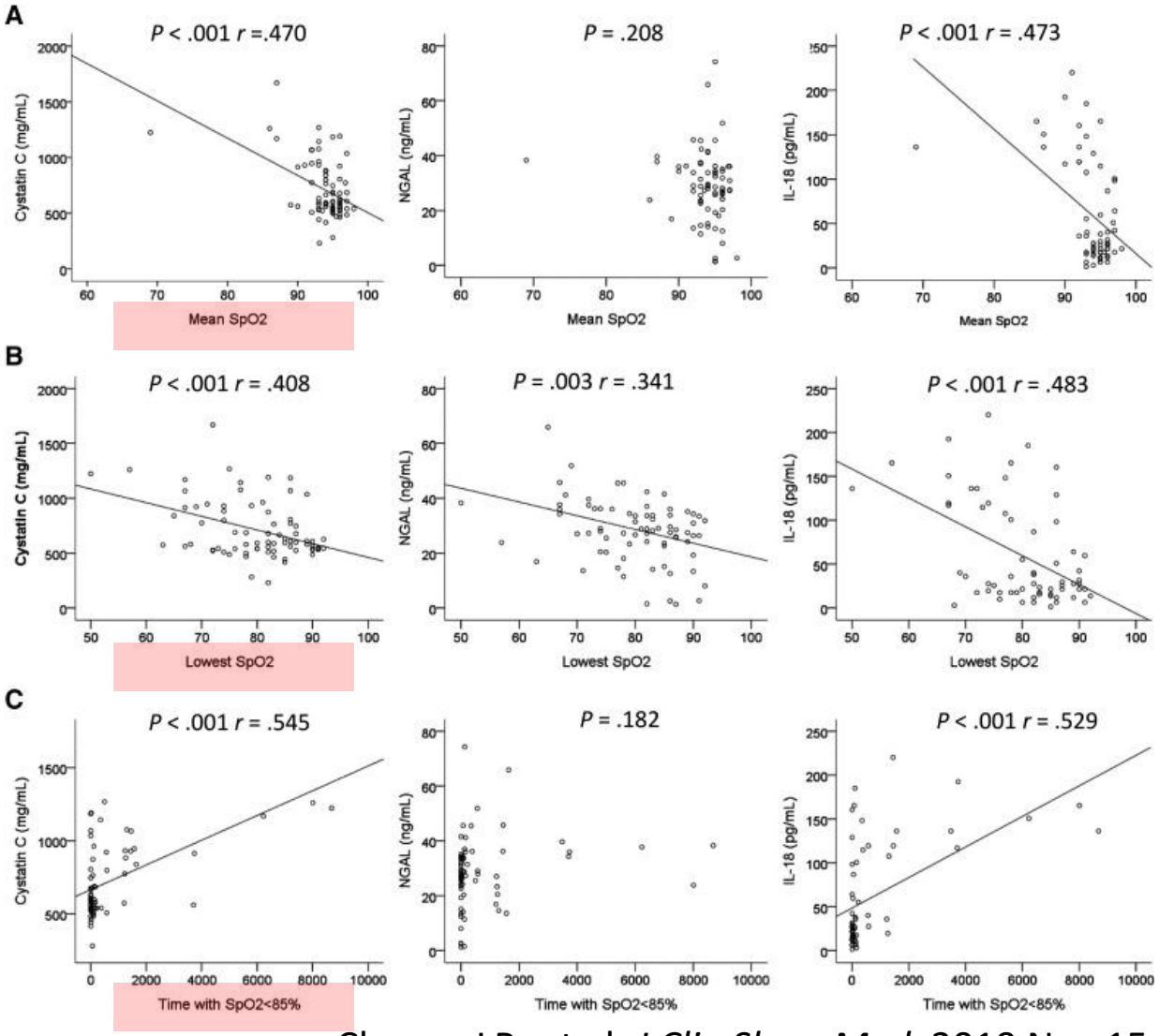
Table 3—Demographic data and change in acute kidney injury markers stratified by CPAP adherence.

	Poor Adherence (n = 34)	Good Adherence (n = 21)	*P*
Male (%)	93	91	1.00
Hypertension (%)	64	72	.59
Age (years)	44.6 ± 1.8	46.6 ± 1.6	.41
BMI (kg/m^2)	30.1 ± 0.8	29.7 ± 0.8	.70
AHI (events/h)	59.7 ± 4.5	64.8 ± 4.7	.44
Creatinine (mg/dL)	1.0 ± 0.2	0.9 ± 0.3	.82
CPAP adherence rate (%)	19.6 ± 2.9	80.9 ± 2.5	< .01
Change in acute kidney injury markers			
UACR (mg/g)	−9.2 ± 48.9	−5.3 ± 10.5*	
NGAL (ng/mL)	−1.9 ± 22.5	−1.7 ± 28.0	
Cystatin C (ng/mL)	62.6 ± 211.9	55.9 ± 165.9	
IL-18 (pg/mL)	−24.6 ± 91.3	−25.8 ± 56.2*	

Values presented as mean ± standard error of the mean. * = $P < .05$ versus baseline. AHI = apnea-hypopnea index, BMI = body mass index, CPAP = continuous positive airway pressure, IL-18 = interleukin-18, NGAL = neutrophil gelatinase-associated lipocalin, UACR = urinary albumin-creatinine ratio.

Chuang LP, et al. *J Clin Sleep Med.* 2019 Feb 15;15(2):207-213.

Hypoxia and AKI Marker



Chuang LP, et al. *J Clin Sleep Med*. 2019 Nov 15;15(11):1697-1698.

Conclusion

- Endothelium damage in obstructive sleep apnea
  - ➔Participant in many comorbidities
- Biomarkers of endothelium damage
  - Cardiovascular
    - ➔MMP9, Chemotaxis(MCP-1, CCR2, CCR5), Vascular dilatation (NO, Glutaminase, Arginase)…..
  - Renal
    - ➔Albuminuria, Acute kidney injury(NGAL, Cystatin C, IL-18)…..

Thank you for your attention!

Dr. Ning-Hung Chen

Prof. Jong-Hwei S. Pang

Prof. Allen I. Pack

Dr. Diane Lim