FMC Sleep and Respiration Rounds

Presented By

Patrick Hanly, MD, FRCPC, D, ABSM

Director, FMC Sleep Centre

University of Calgary

Wednesday, October 2, 2019

Alberta Health Services

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Sleep and Respiration Rounds

Sleep Apnea in Patients with Renal Failure

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Wednesday, October 2, 2019
Lunch: 11:30am
Presentation: 12:00-1:00pm

Room 01500
O'Brien Centre
Health Sciences Centre

The Sleep and Respiration Rounds in the division of Respiratory Medicine at the University of Calgary is a self-approved group learning activity (Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada.

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Sleep Apnea and Kidney Disease
-A bidirectional relationship

Patrick J Hanly MD, FRCPC, DABSM

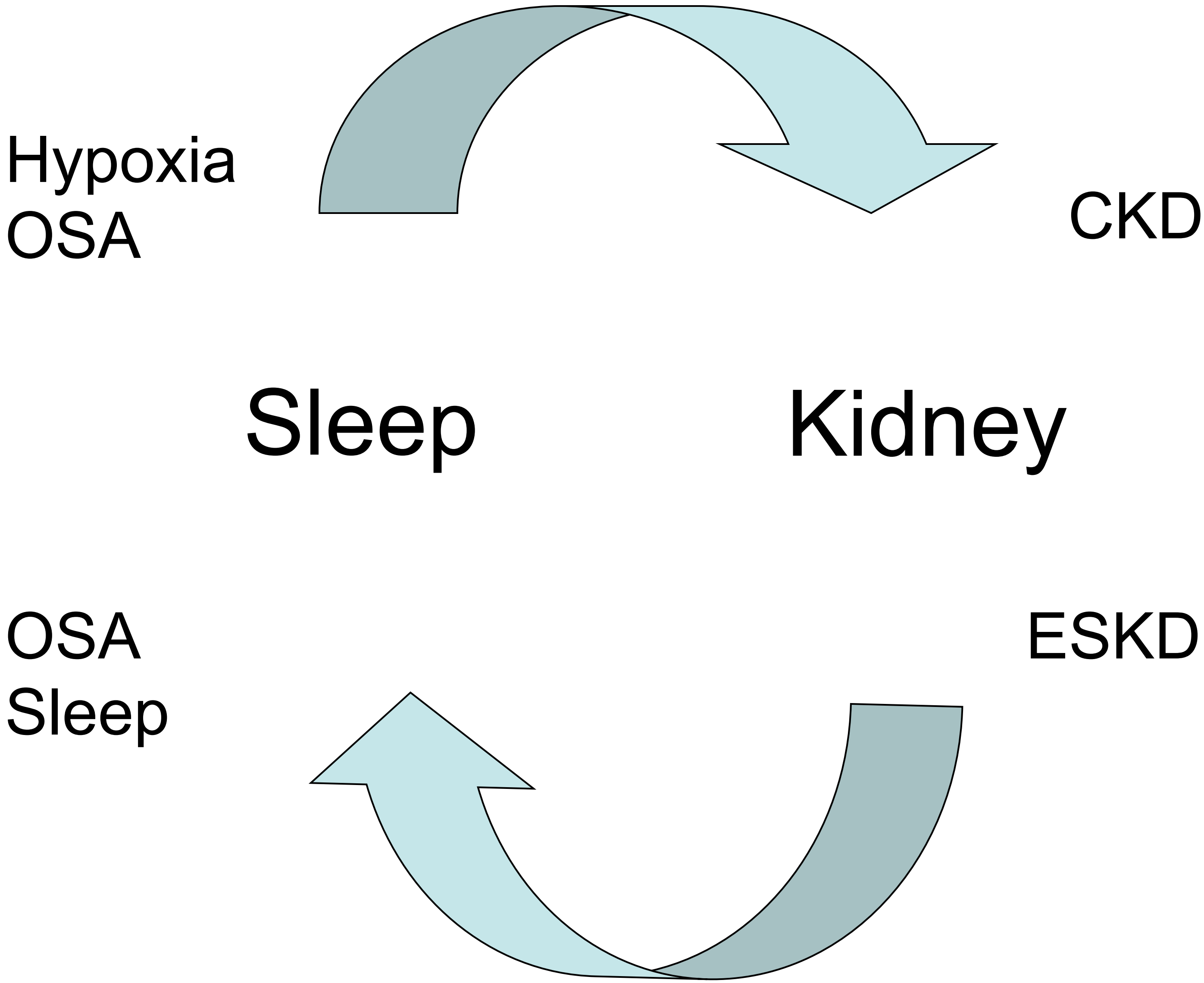
Sleep Centre, Foothills Medical Centre,
University of Calgary

WSS, September 2019

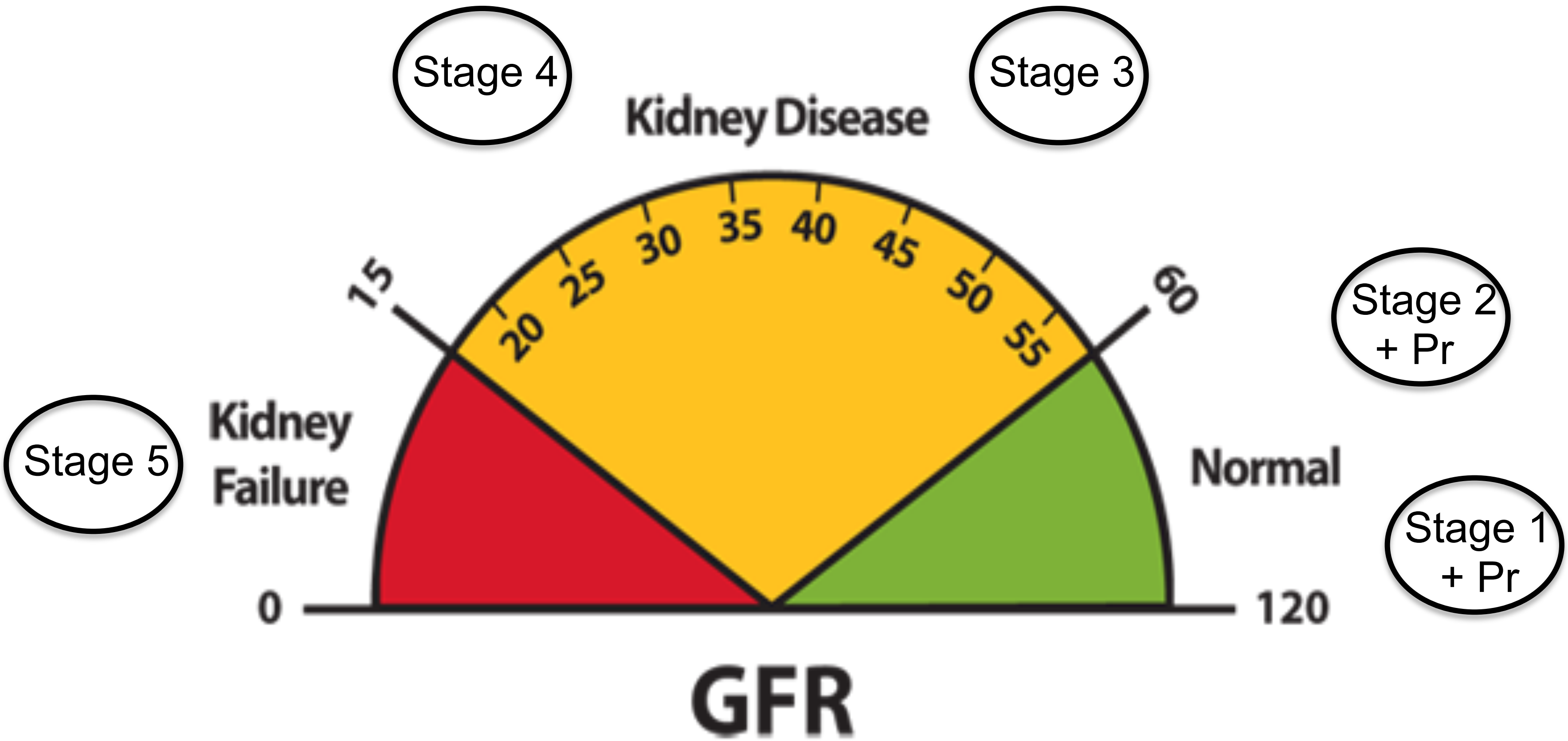
Disclosures

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	Philips Respironics (equipment and financial)
Consultant	Dream Sleep Respiratory Services, BresoTec
Speakers' Bureaus	
Financial support	
Other	

Sleep and Renal Function: *Bidirectional Relationship*

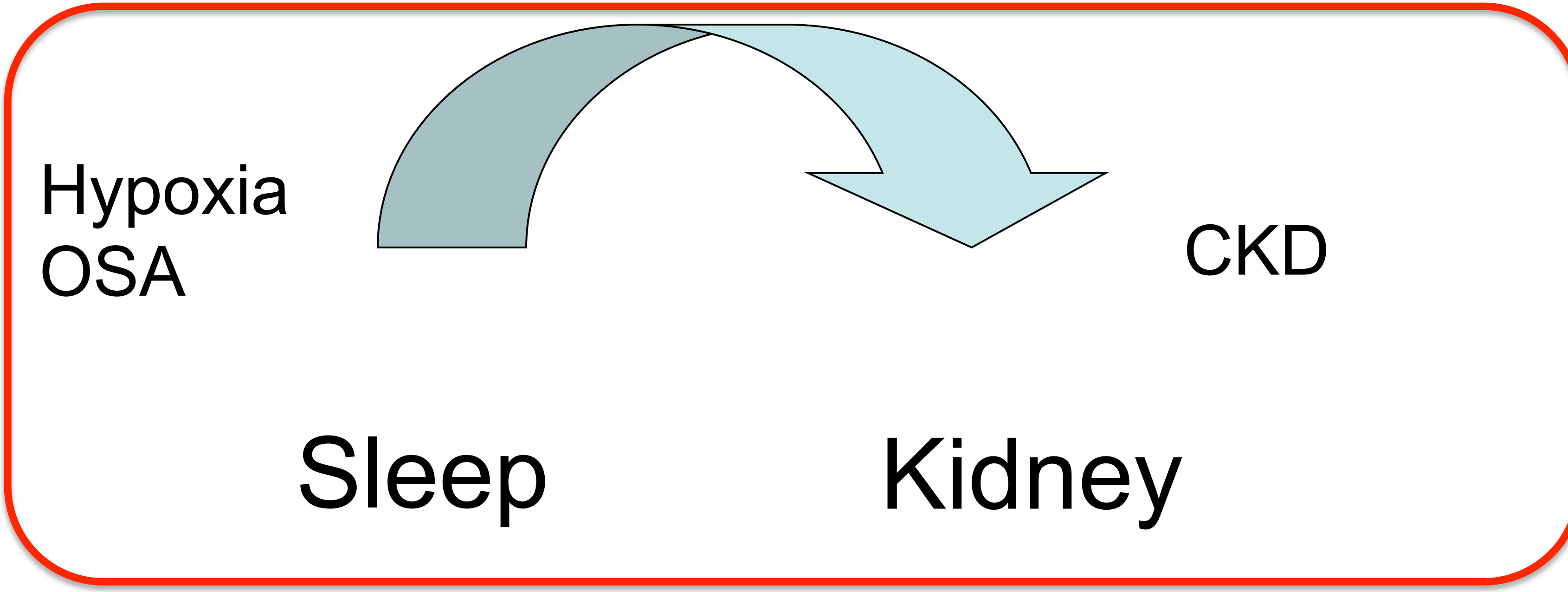


Chronic Kidney Disease (CKD): Definition



GFR = Glomerular Filtration Rate (ml/min/1.73m^2)

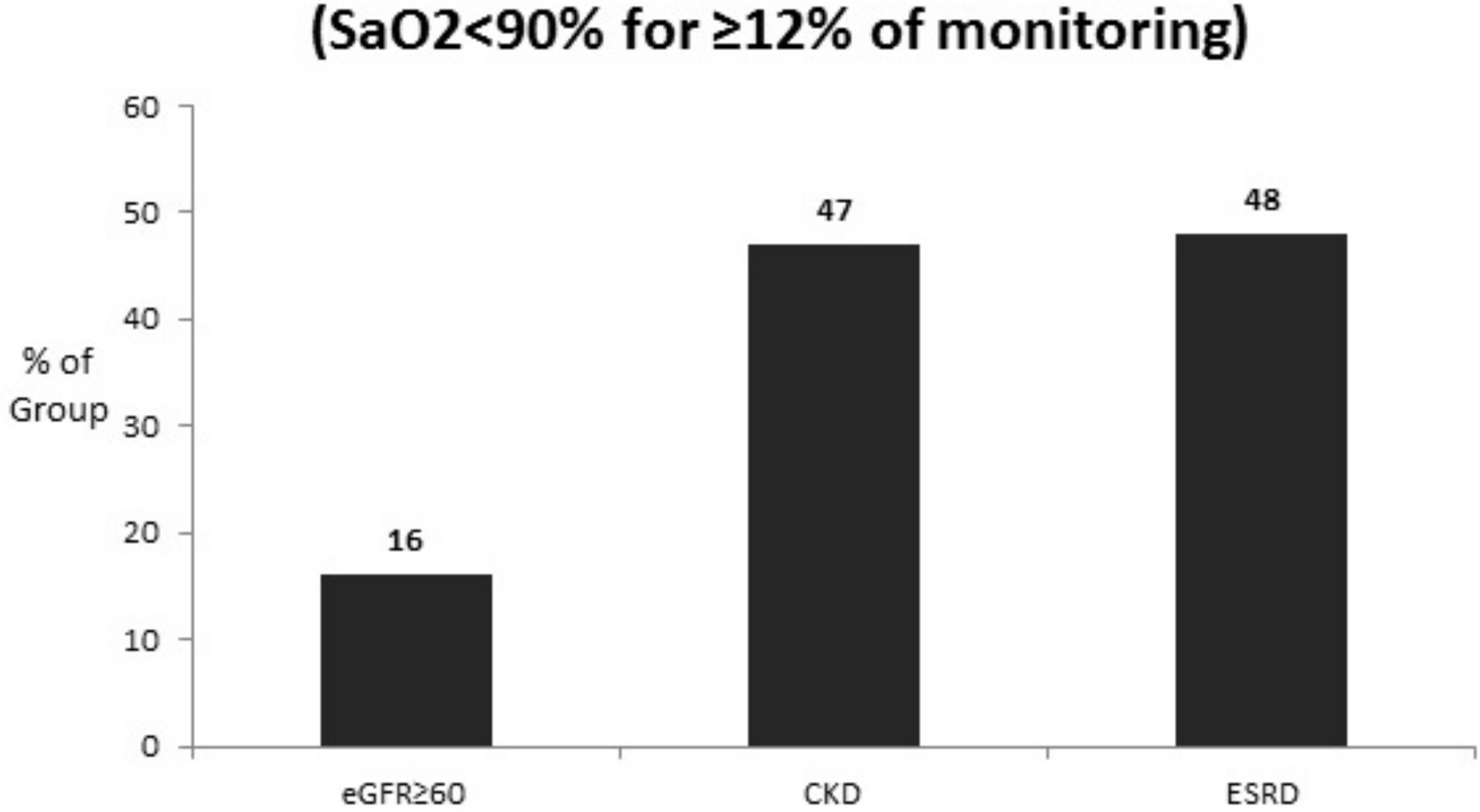
Sleep and Renal Function: *Bidirectional Relationship*



- Biological plausibility
- Association vs Causality

OSA is common in CKD

Nocturnal Hypoxemia



Nicholl, Chest 2012;141:1422-1430

Animal Model: *Hypoxemia causes intra-renal hypoxia*

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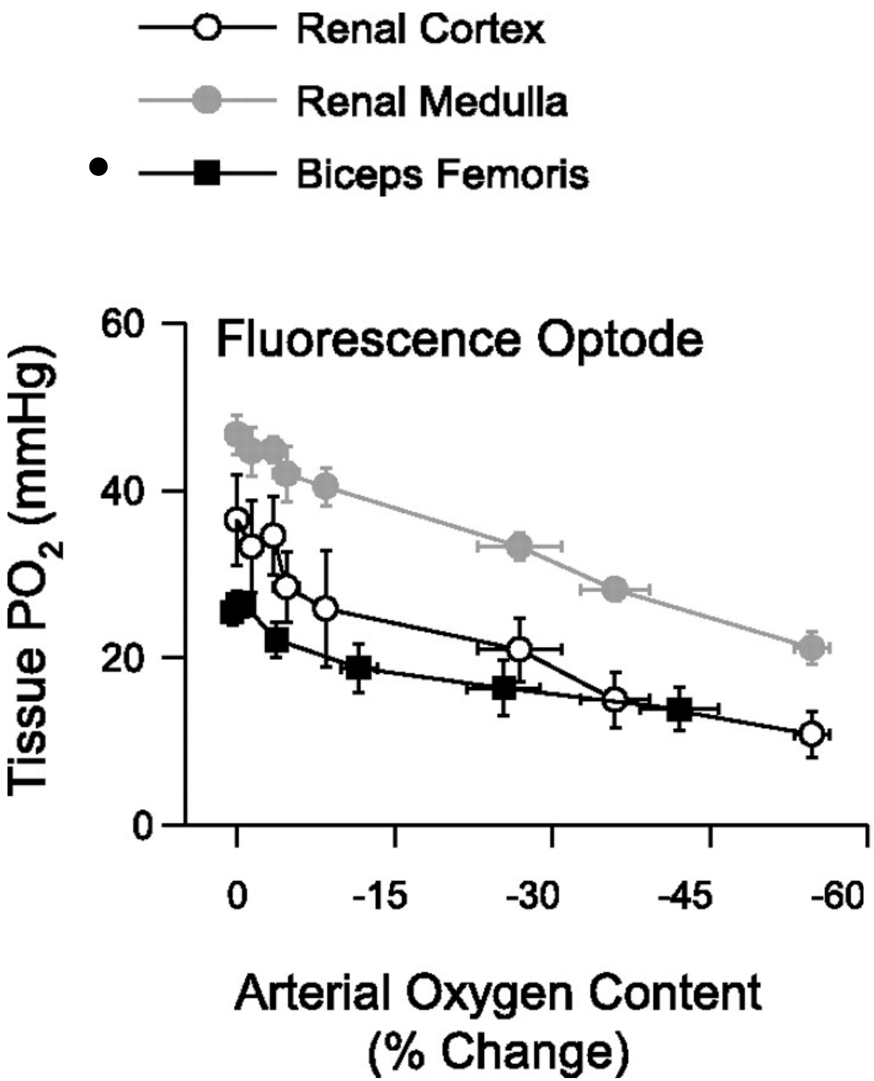
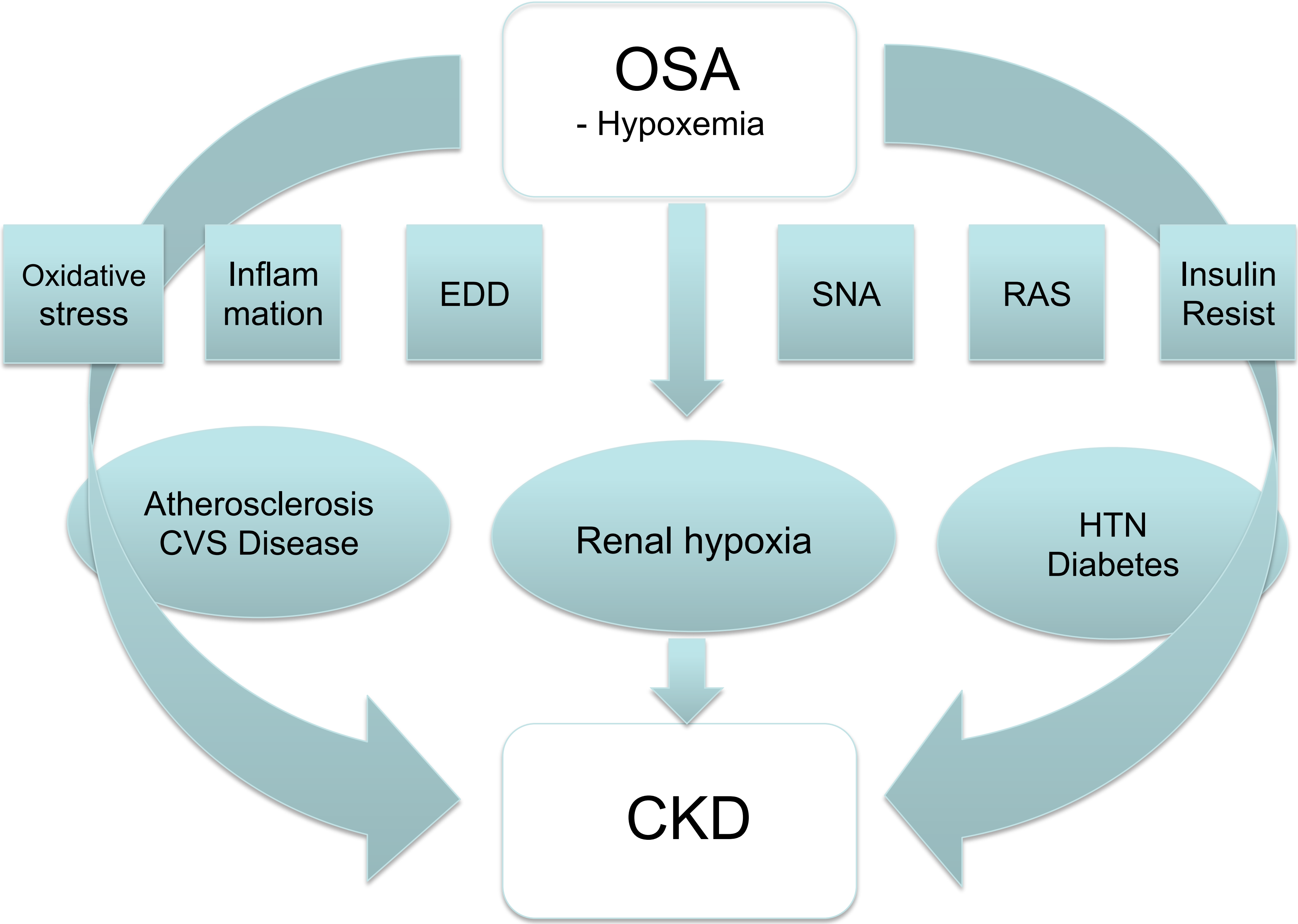
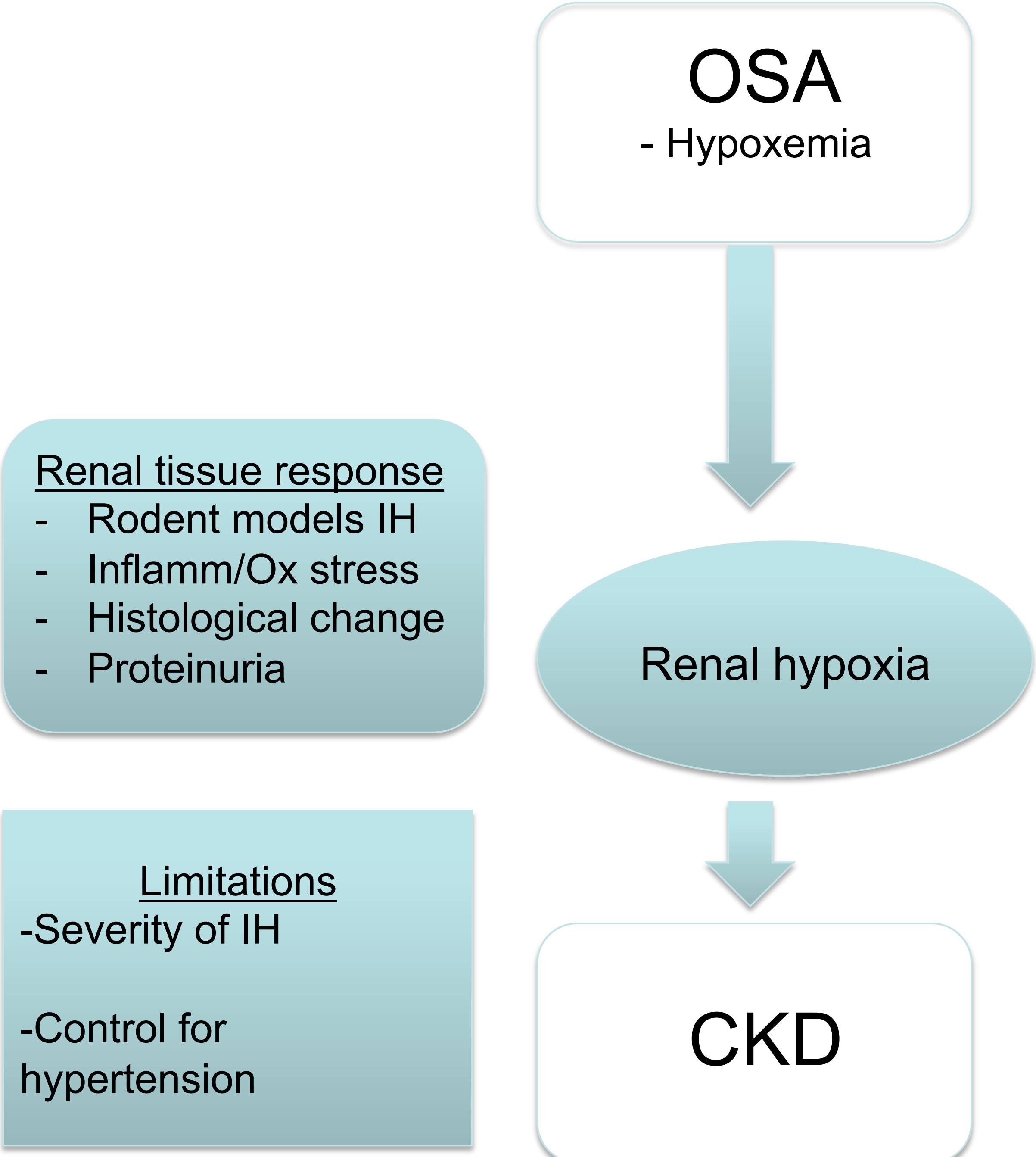


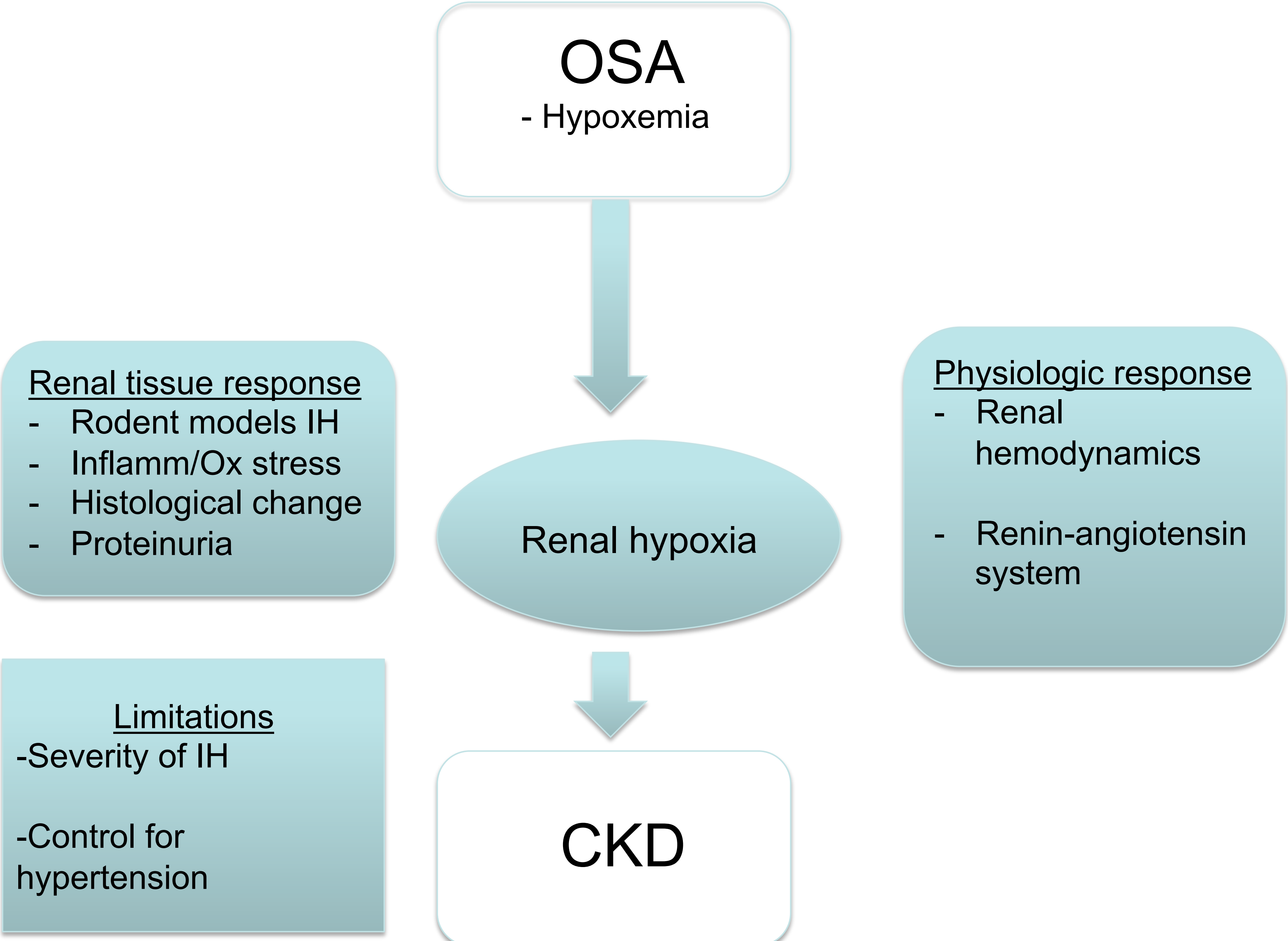
- Ventilated rabbit, denervated kidney
- Systemic hypoxemia / Reduced Do_2
- Tissue Po_2 fell progressively (detected when CaO_2 fell 4-8%)
- Vo_2 remained stable despite reduced Do_2
- No hyperemic response to hypoxia

Kidney susceptible to tissue hypoxia, even during mild hypoxemia

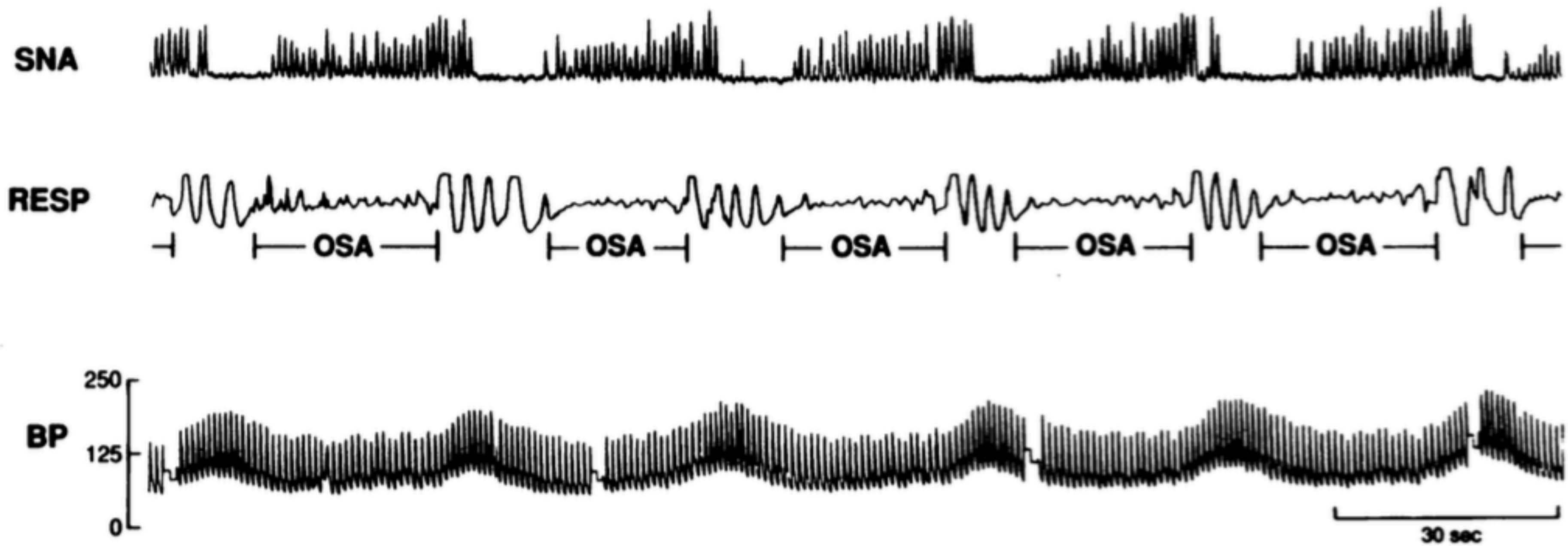
Evans, Am J Physiol Regul Integr Comp Physiol 2011;300:R931-R940


OSA
- Hypoxemia
Oxidative stress
Inflam mation
EDD
SNA
RAS
Insulin Resist
Atherosclerosis CVS Disease
Renal hypoxia
HTN Diabetes
CKD


OSA
- Hypoxemia
Renal tissue response
- Rodent models IH
- Inflamm/Ox stress
- Histological change
- Proteinuria
Renal hypoxia
Limitations
-Severity of IH
-Control for hypertension
CKD


OSA
- Hypoxemia
Renal tissue response
- Rodent models IH
- Inflamm/Ox stress
- Histological change
- Proteinuria
Renal hypoxia
Physiologic response
- Renal hemodynamics
- Renin-angiotensin system
Limitations
-Severity of IH
-Control for hypertension
CKD

OSA: Sympathetic Nervous System (SNA)

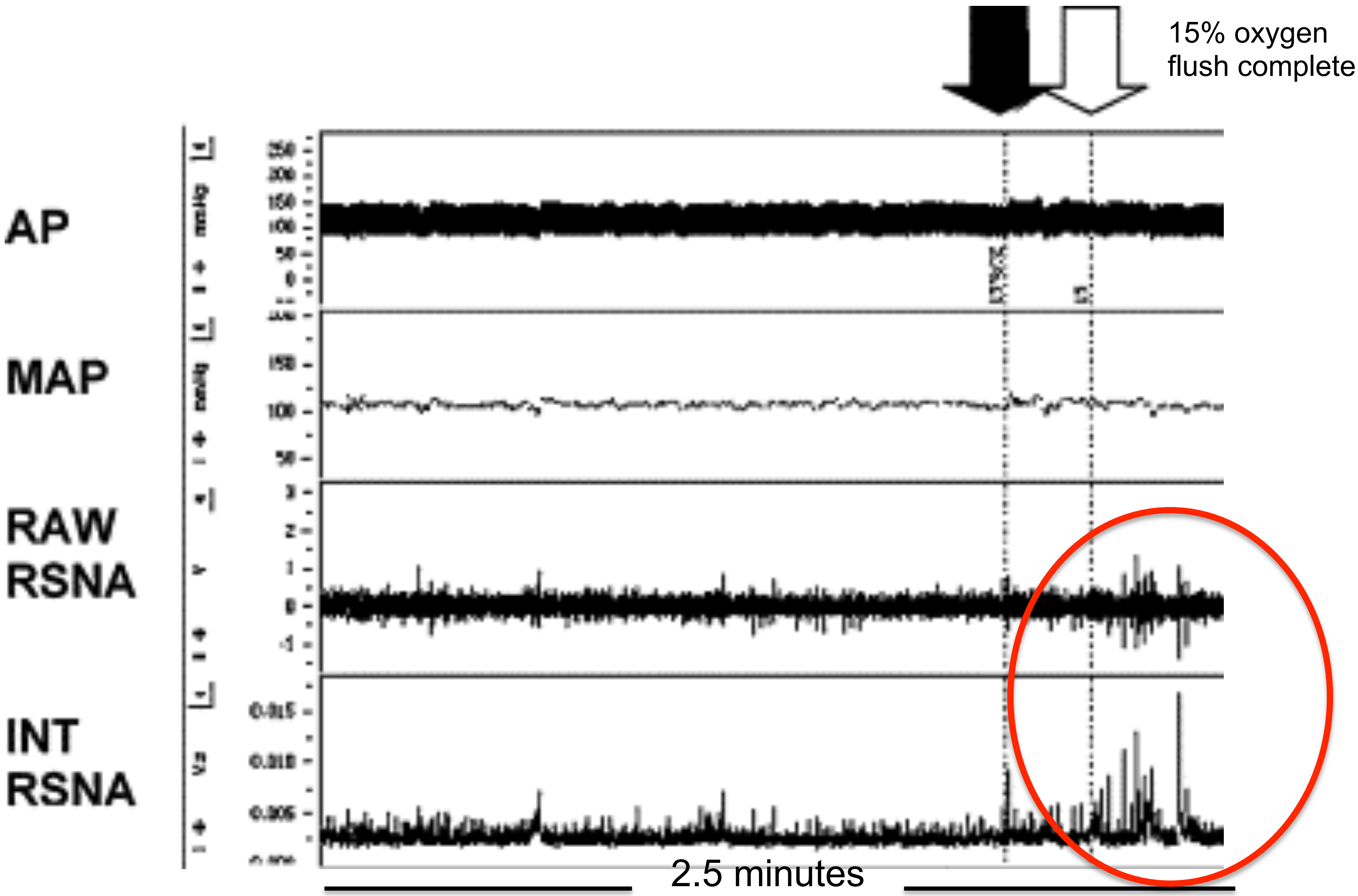


Does intermittent hypoxia effect SNA in the kidney?

Somers, J Clin Invest, 1995; 96:1896-1904

Rats: Chronic Intermittent Hypoxia (CIH) x 3wks, 8hr/day

- Renal SNA (RSNA) response to hypoxia

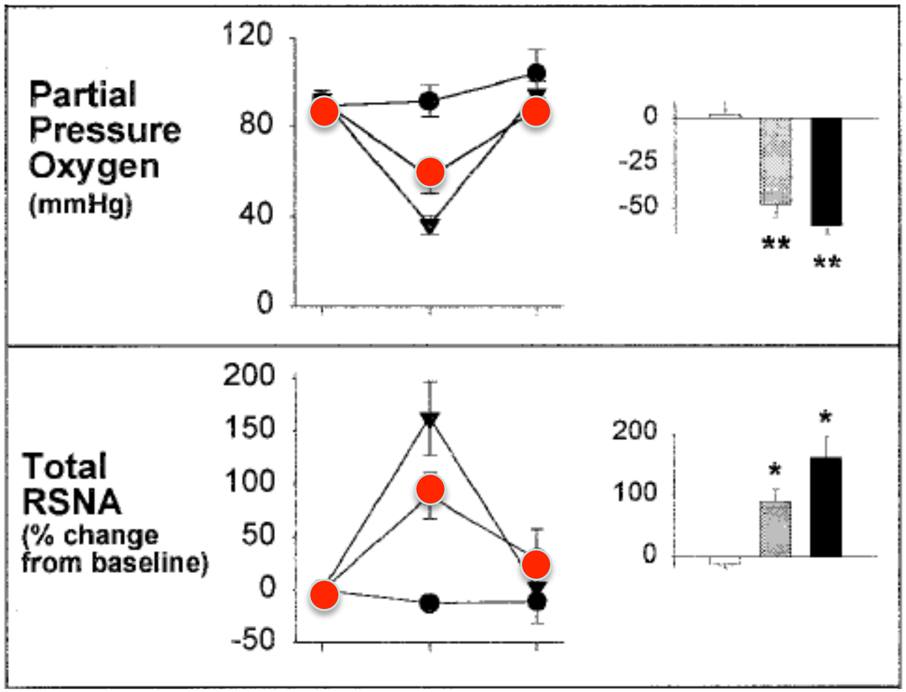


Huang, 2009: Respiratory Physiology & Neurobiology, 166,:102–106

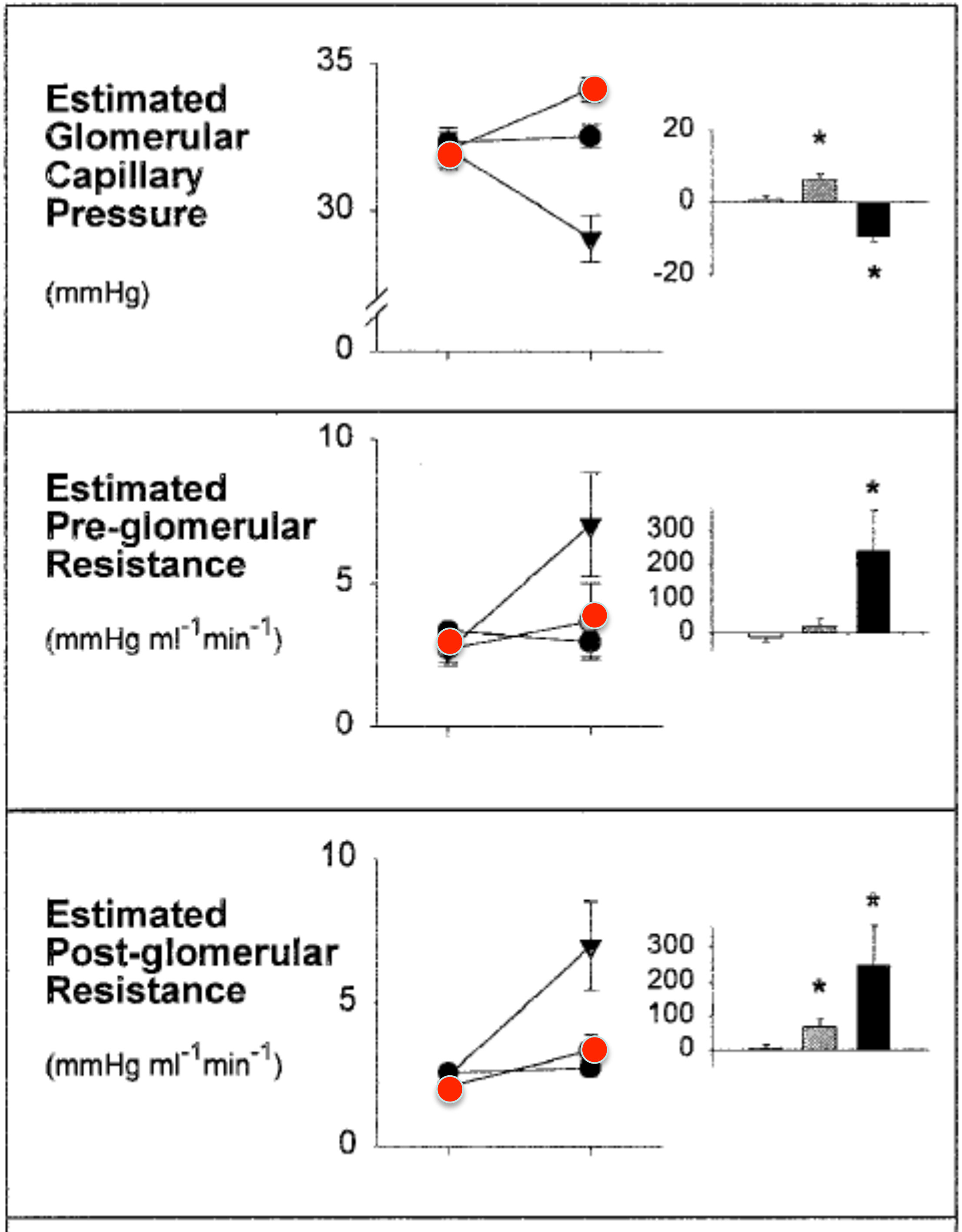
Hypoxia: RSNA: Renal HD

Denton, J Am Soc Nephrol, 13:27-34,2002

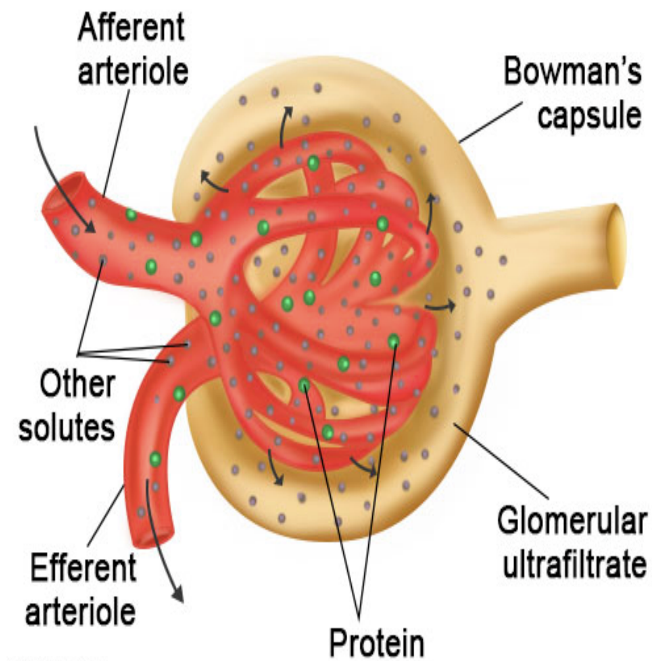
- Rabbit model (ventilated)
  - Room air, Moderate hypoxia(●), Severe hypoxia
- Left kidney exposed
  - Renal nerve recording (RSNA)
  - Glomerular resistance: Pre-Glom & Post Glom



Moderate Hypoxia



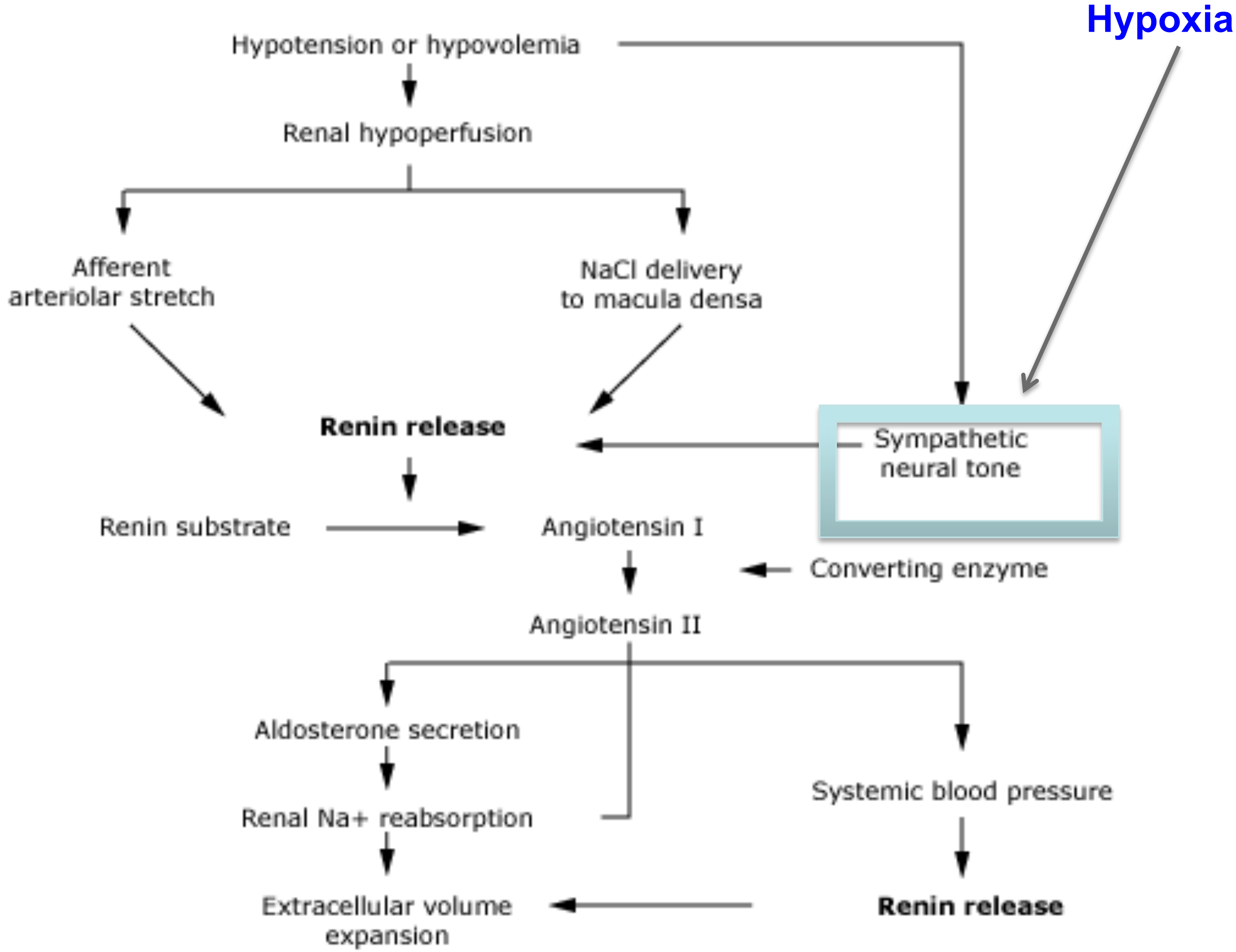
Glom pressure ↑



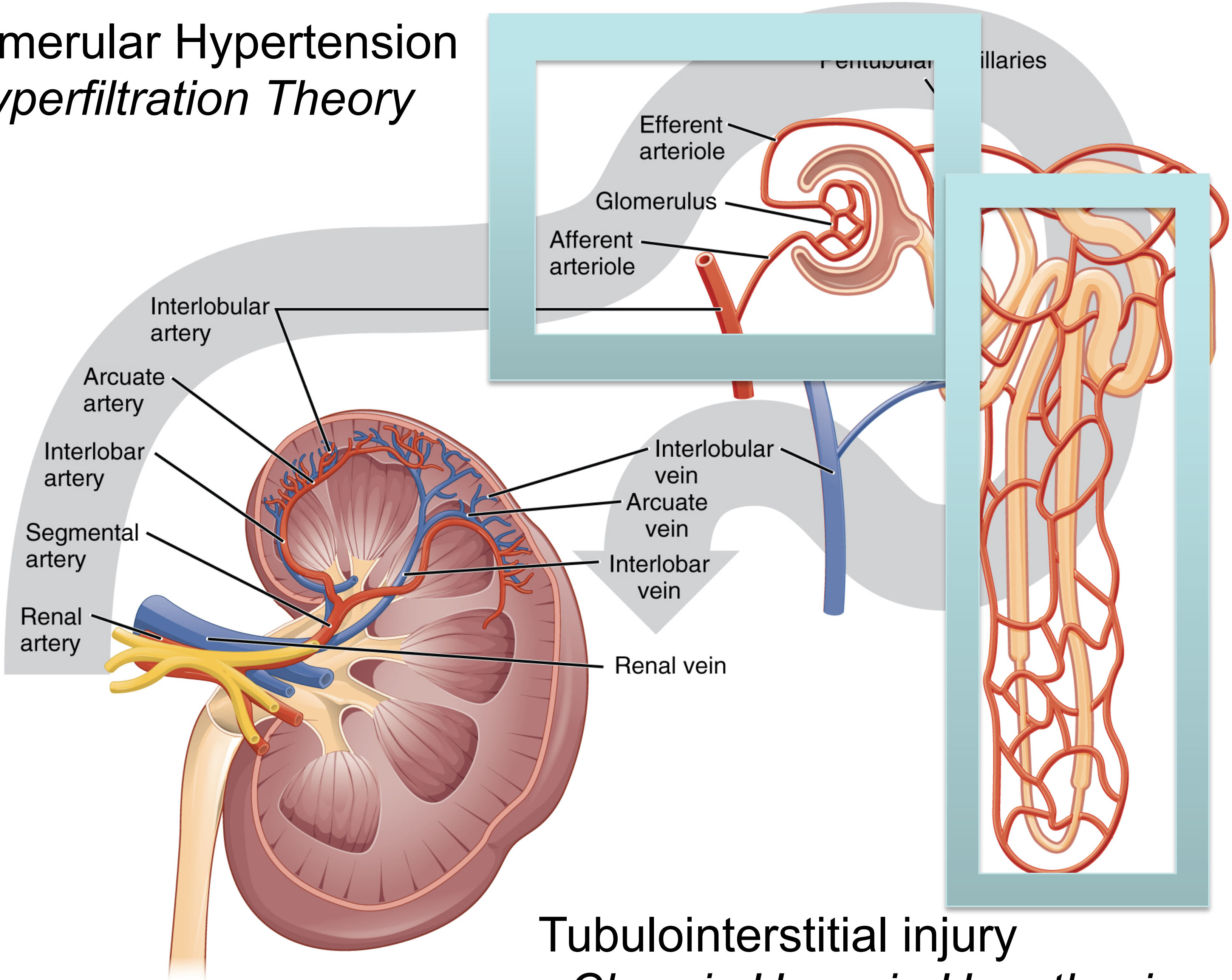
Post Glom R ↑ 70%

Denton, J Am Soc Nephrol, 13:27-34,2002

Hypoxia and Renin-Angiotensin System (RAS)

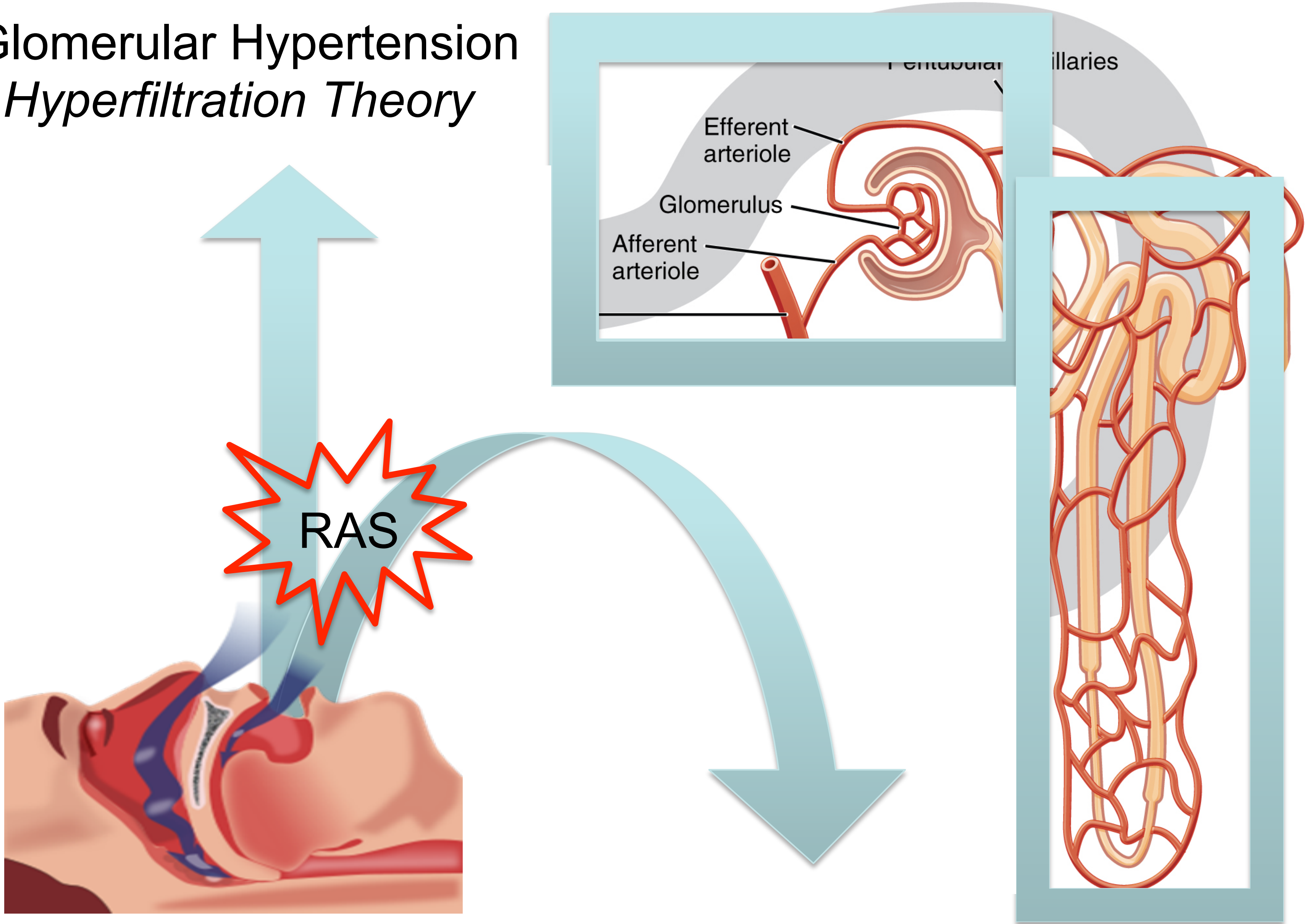


Glomerular Hypertension
- *Hyperfiltration Theory*



Tubulointerstitial injury
- *Chronic Hypoxia Hypothesis*

Glomerular Hypertension
- *Hyperfiltration Theory*

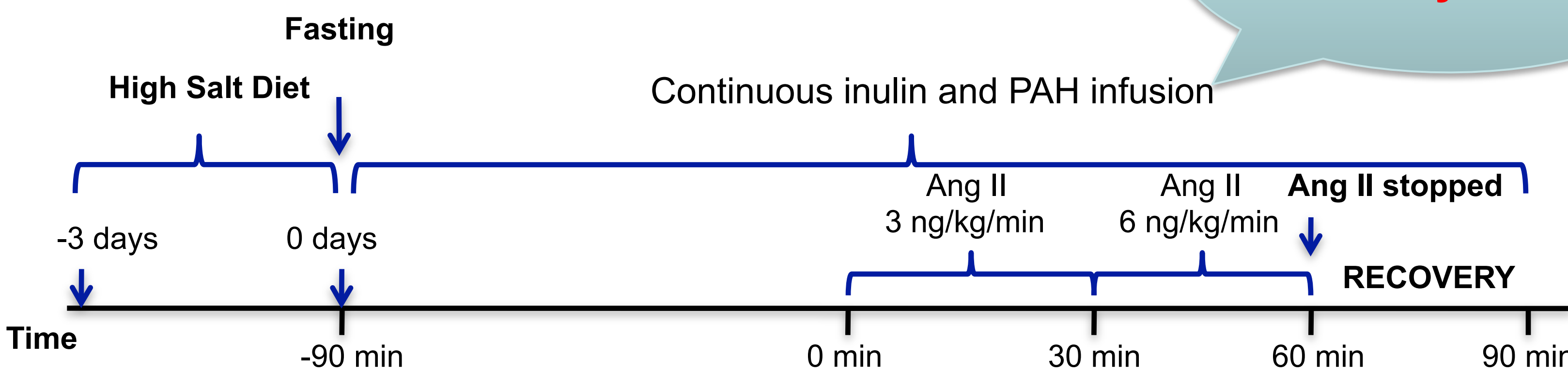


OSA

Tubulointerstitial injury
- *Chronic Hypoxia Hypothesis*

Renal Hemodynamics & Renal RAS: St

Renal Hemodynamics



Renal RAS

Renal Hemodynamics & Renal RAS

- Renal hemodynamics
  - Baseline RPF, GFR, FF (GFR/RPF)
    - ***FF = Surrogate marker of glomerular pressure***
- Renal RAS
  - RPF response to AngII
    - ***ΔRPF = Surrogate marker of renal RAS activity***

Filtration Fraction in OSA Patients & Obese Controls

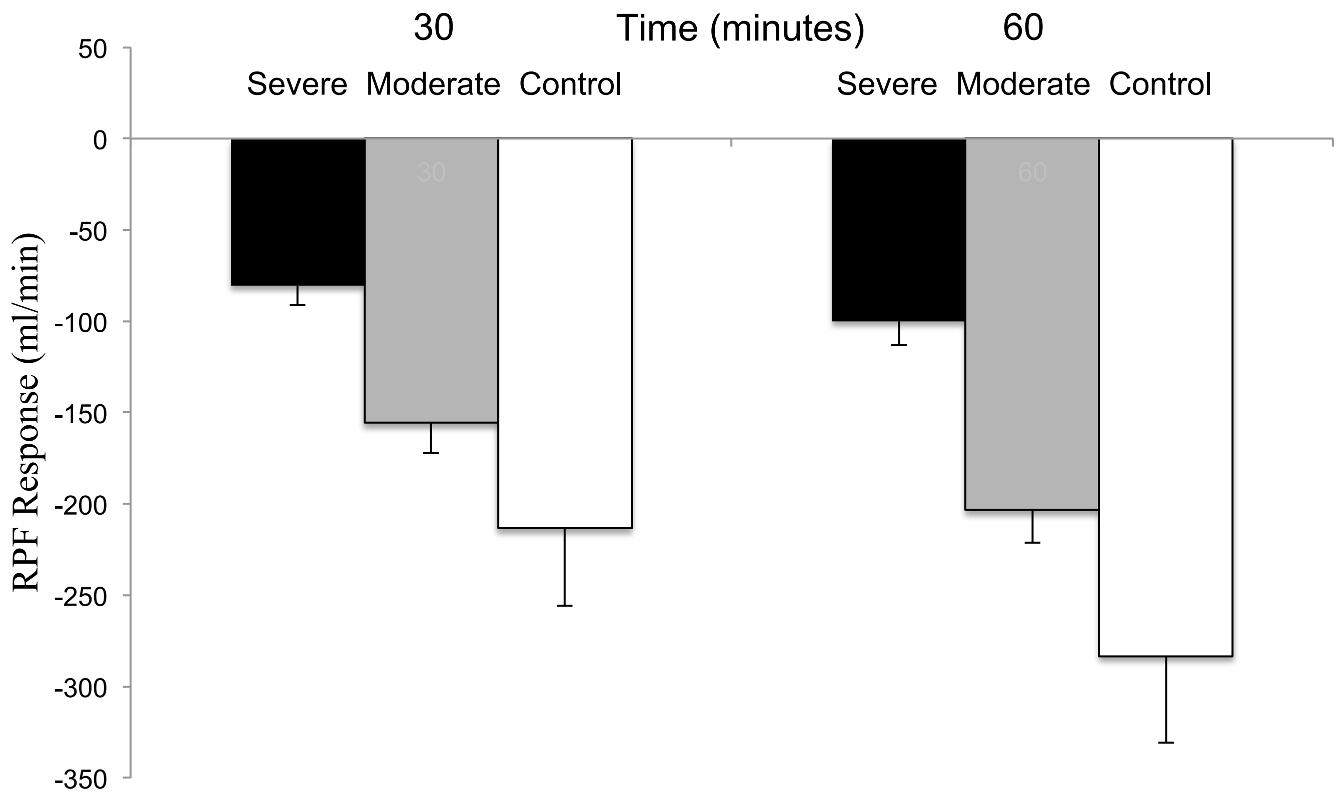
Zalucky, 2015; Am J Respir Crit Care Med 192:873-80

	Severe	Moderate	Control
# patients	14	17	12
Age (yrs)	47 ± 11	49 ± 10	42 ± 11
Men (%)	57	71	33
% Caucasian	93	59	100
BMI (kg/m2)	**43 ± 5.5***	**33 ± 6.7**	**39 ± 7.5**
RDI (/hr)	64 ± 26*	40.4 ± 18.6†	5 ± 2.3
Mean SaO2 (%)	84 ± 4.4*	91 ± 0.2†	93 ± 1.4
SaO2<90% (%)	**77 ± 14.7***	**24.6 ±1 0.3†**	**2.2 ± 3.8**
ERPF (ml/min)	674 ± 88	689 ± 121	805 ± 221
GFR (ml/min)	106 ± 9.6	126 ± 37.8	107 ± 15.2
FF	**16 ± 1.5†**	**19 ± 6.6†**	**14 ± 2.6**

OSA is associated with Glomerular Hypertension

Renal RAS in OSA Patients & Obese Controls

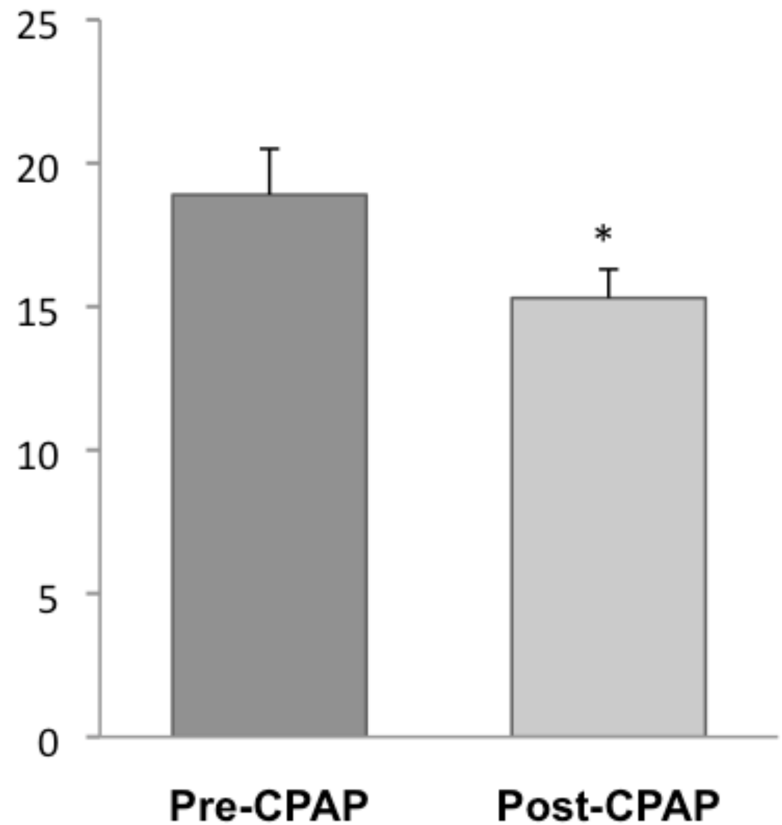
- Response of RPF to AngII infusion



Renal RAS is up-regulated in OSA independent of obesity, and in proportion to the severity of hypoxia

Impact of CPAP: Filtration Fraction

Filtration Fraction (%)

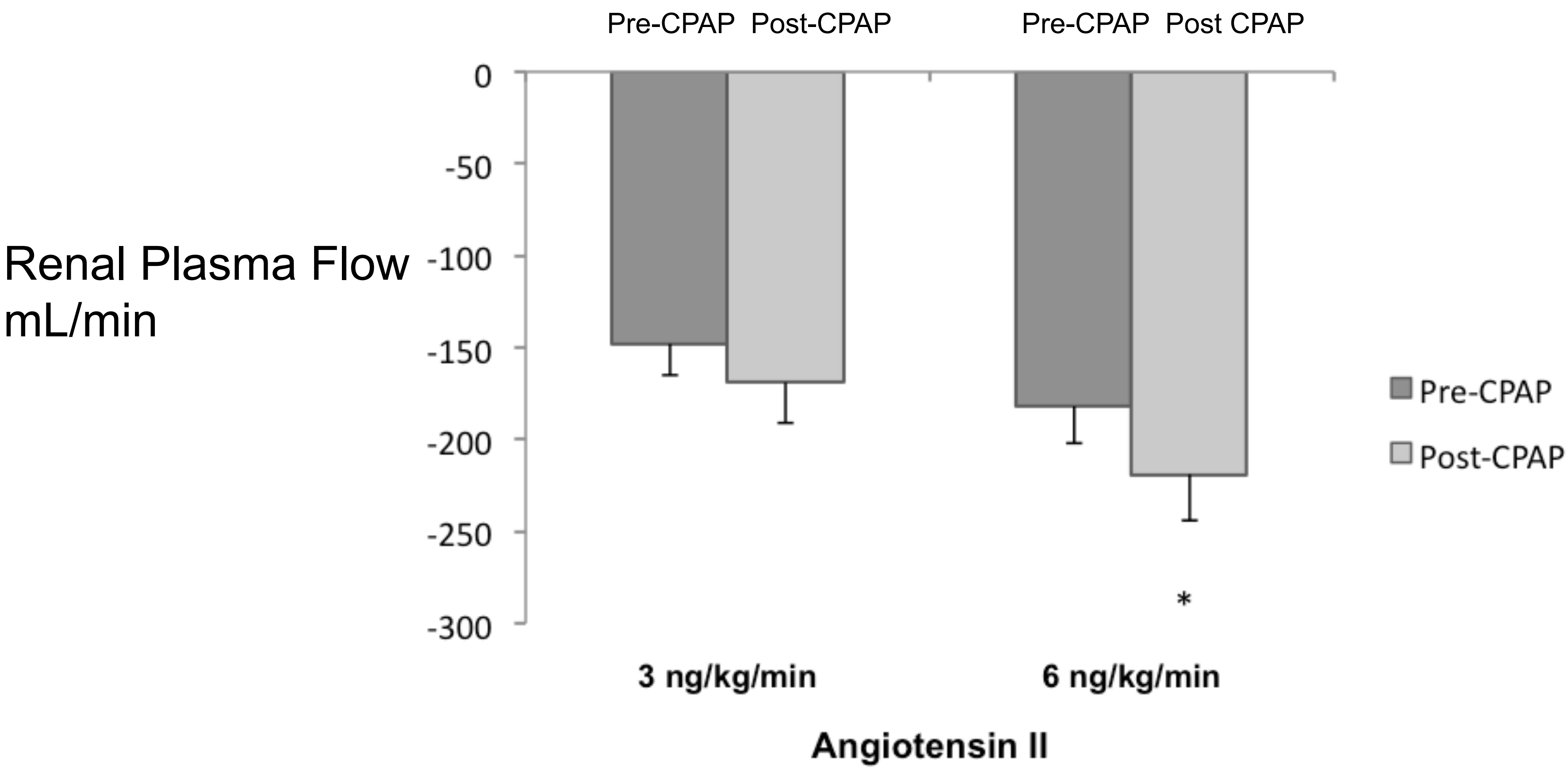


Reduced FF = Decreased Glomerular Pressure

Nicholl, Am J Respir Crit Care Med 2014;190:572-580

Impact of CPAP: Renal RAS

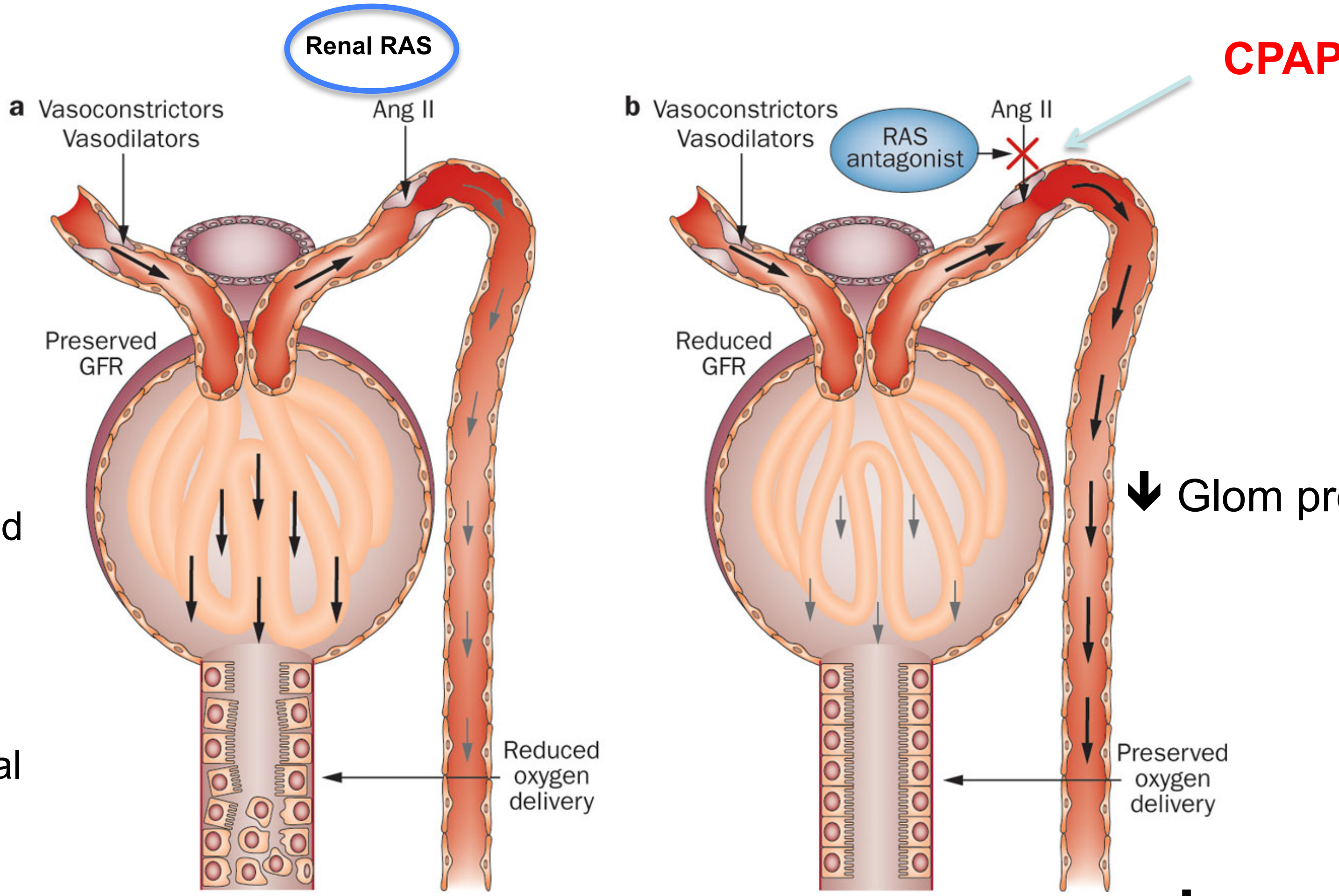
- *Response of RPF to AngII infusion*



Greater response to AngII (post CPAP)
= Renal RAS down-regulated by CPAP

Nicholl, Am J Respir Crit Care Med 2014;190:572-580

Effect of OSA on the Kidney



Glom HTN
Hyperfiltrartion

Protein overload

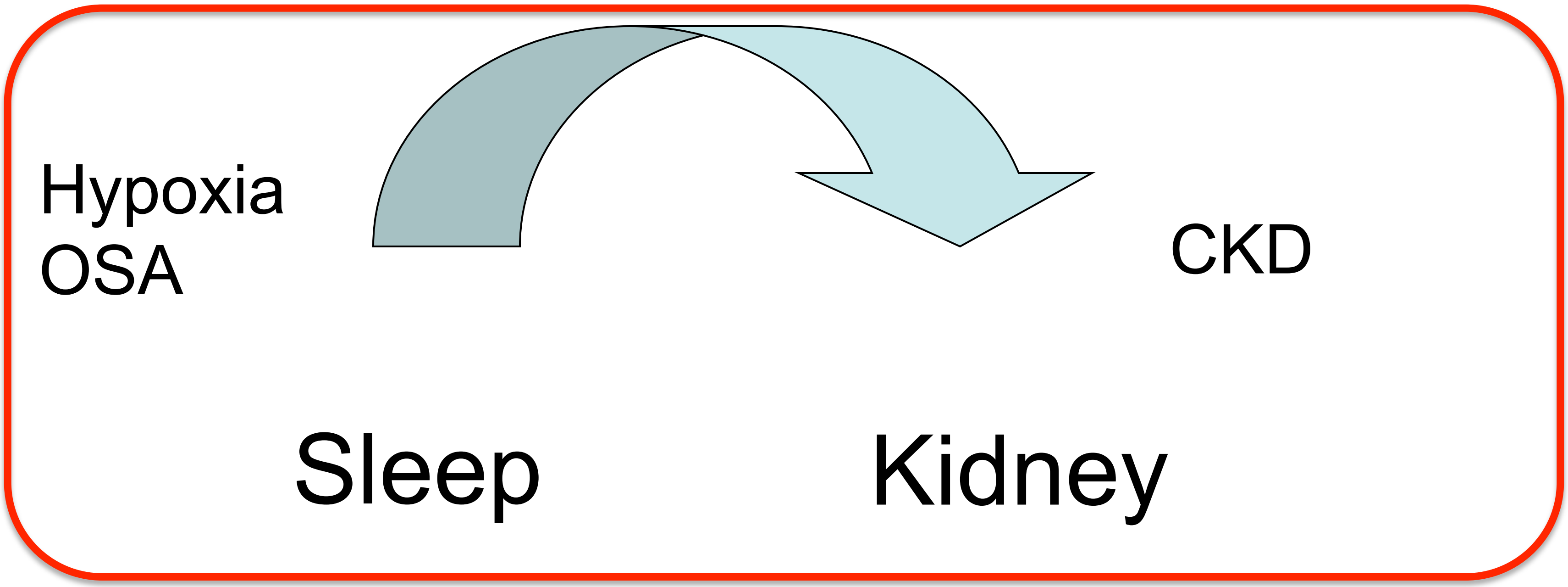
Tubulointerstitial
injury

↓ Glom pressure

↓ Hypoxia

Perazella, M. A. & Coca, S. G. (2013) *Nat. Rev. Nephrol.*

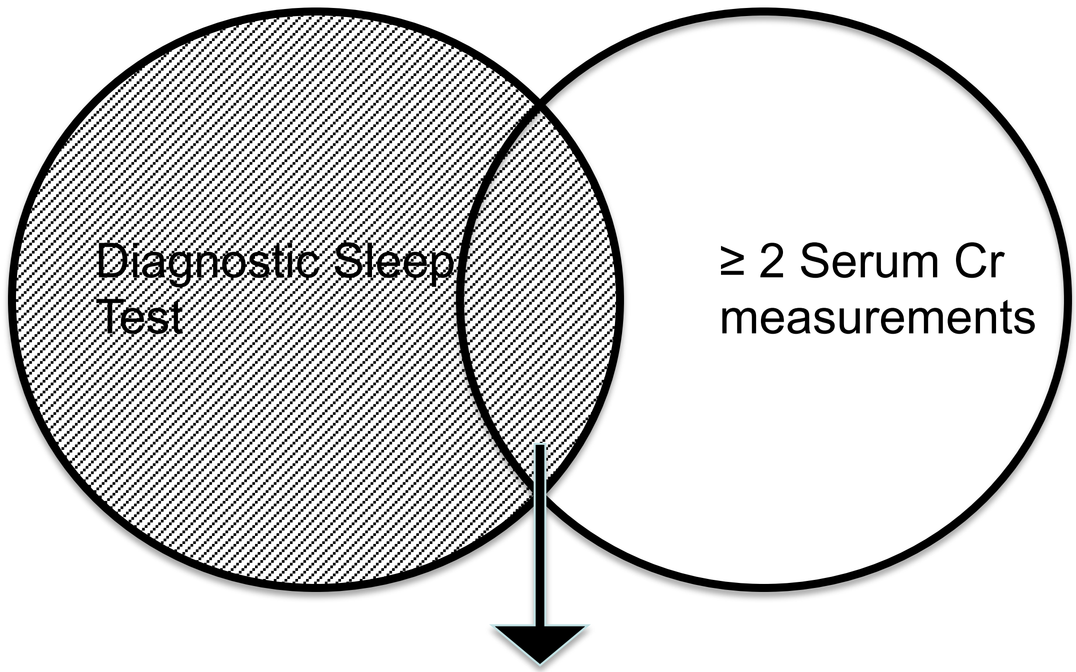
Sleep and Renal Function: *Bidirectional Relationship*



- Biological plausibility
- Association vs Causality

Is OSA associated with CKD progression ?

Sleep Centre Database



Alberta Kidney Disease Network

Nocturnal Hypoxemia
- SaO2<90% for ≥ 12% recording time

→

Renal Function
- Rapid Decline GFR ($\geq 4 ml/min/1.73 m^2/yr$)

Ahmed, PLoS One 2011;6:19029

Is OSA associated with CKD progression ?

- 858 patients, 44% had nocturnal hypoxemia
- Rapid Decline GFR (≥4ml/min/1.73m^2/yr)

	Unadjusted Model OR [95% CI]	Multivariate adjusted model† OR [95% CI]	Multivariate adjusted model‡ OR [95% CI]
Nocturnal Hypoxia	6.32 [3.03-13.20]	3.38 [1.53-7.45]	2.89 [1.25-6.67]

*‡ Adjusted for RDI, age, BMI, diabetes and heart failure

Ahmed, PLoS One 2011;6:19029

OSA: Risk of Incident CKD

- Cohort definition
  - eGFR > 60 *without* a diagnosis of OSA

- Exposure (Oct 2004 – Sept 2006)
  - Incident OSA ± CPAP

- Outcomes
  - *Incident CKD:* eGFR<60 twice, and >25% decrease vs baseline
  - *Rate of decline in renal function*
    - Slope of change in eGFR
    - Rapid deterioration in eGFR (>5 ml/min/1.73m^2/y)
- Follow up period (median 7.74 yrs)

Molnar, Thorax 70:888-895, 2015

OSA: Risk of Incident CKD

- Three groups: No OSA OSA OSA+CPAP

- Incident CKD
  - Event rate 10% 25% 29%
  - *HR (OSA, no tx) 2.27 (CI 2.19-2.36)*
  - *HR (OSA+CPAP) 2.79 (CI 2.48-3.13)*

- Decline in renal function
  - eGFR slope -0.41 -0.61 -0.87

- Rapid decline
  - *OR (OSA, no tx) 1.3 (CI 1.24-1.35)*
  - *OR (OSA+CPAP) 1.28 (CI 1.09-1.5)*

Molnar, Thorax 70:888-895, 2015

CPAP: Impact on renal function

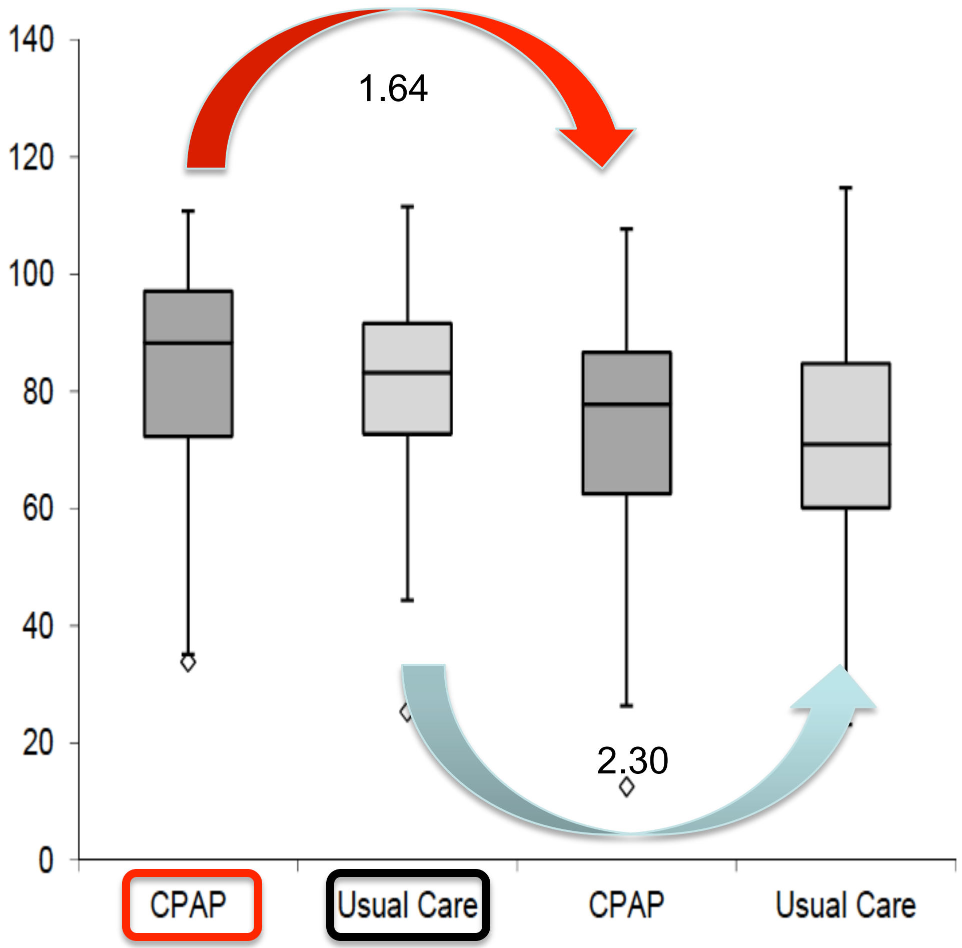
- Sub-study of SAVE (Sleep Apnea & cardioVascular Endpoints) trial
  - 200 pts, AHI 15-29: randomized CPAP vs usual care
  - Follow up: 4.3 (CPAP) and 4.5 (usual care) years
  - Primary outcome: Annual rate of decline of eGFR

- Analysis
  - Intention to treat: CPAP adherence 4±2.6 hrs/night
  - Per protocol: Good CPAP adherence (≥4 hrs/night)
    Poor CPAP adherence (<4 hrs/night)
    No CPAP (usual care)

Loffler, Am J Respir Crit Care Med, 2017;

ΔGFR: Annual Rate of Decline

Annual Change in eGFR (ml/min/1.73m^2)



Baseline

Exit

Loffler, Am J Respir Crit Care Med, 2017;

Sub-study of SAVE: *Limitations*

- Patient population
  - Underpowered for primary outcome
  - Majority (≈ 90%) patients did not have CKD

- Risk for progression of renal failure was low
  - Low prevalence of diabetes (≈ 25%)
  - Low prevalence albuminuria (≈ 10%)

- Renal insult modest
  - Nocturnal hypoxemia mild (rarely < 85%)
  - ACEI's (≈ 90%) and ARB's (≈ 70%)

OSA: Risk of CKD

- *Are we studying the right population?*

- Sleep clinic OSA cohort
  - More symptomatic (sleepiness)
  - More severe hypoxemia ± hypoventilation
- Nephrology clinic
  - More risk factors for CKD
  - Established and active kidney disease

Prevalence of OSA patients *at risk* of CKD progression

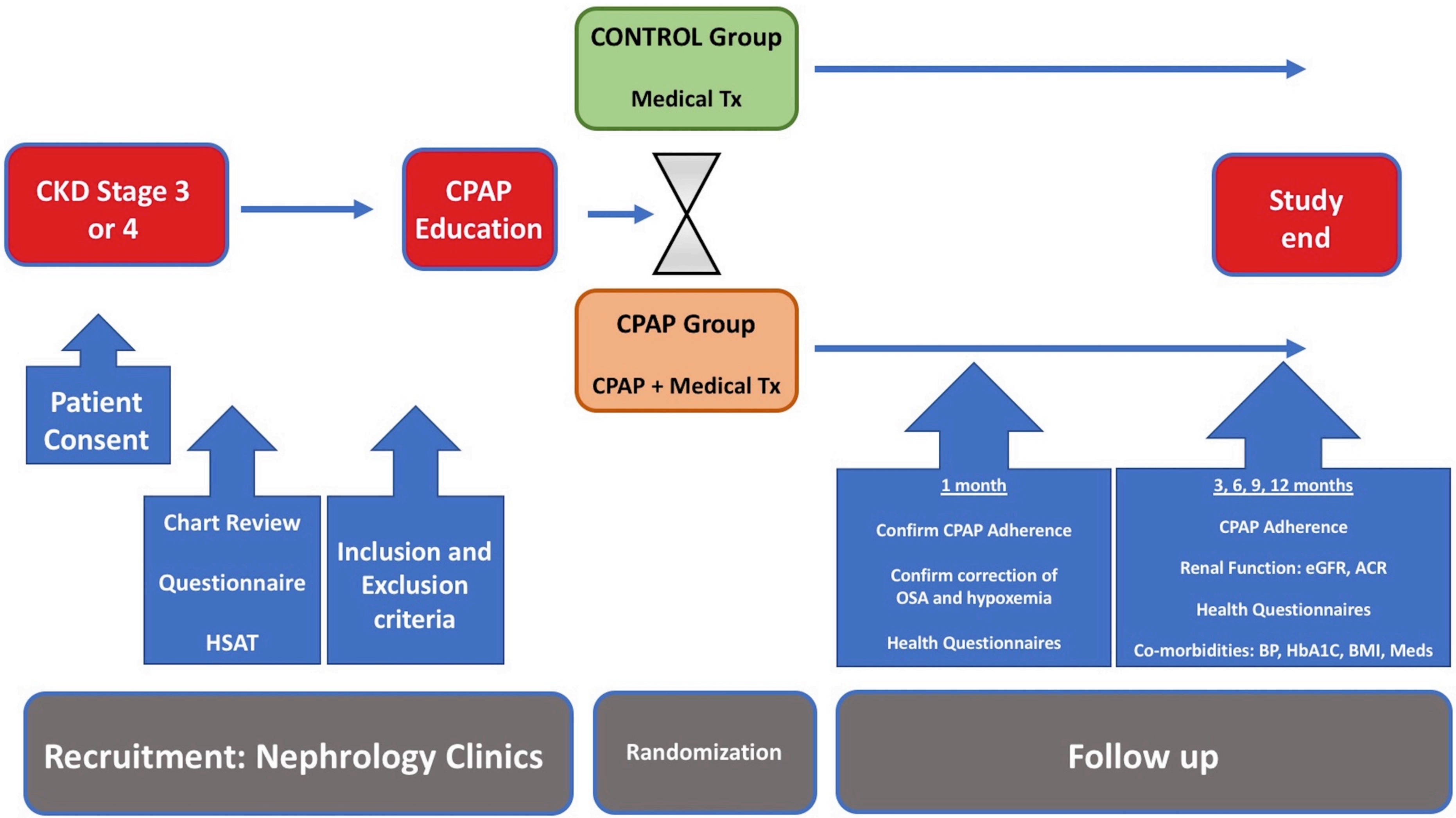
- CSCN OSA Cohort (n=727)

GFR ml/min/1.73m²	Albumin:Creatinine Ratio		
	A1: Normal-to-Mild increase <3 mg/mmol	**A2: Moderate increase** 3-30 mg/mmol	**A3: Severe increase** >30 mg/mmol
≥90	237 (32.6)	52 (7.2)	8 (1.1)
60-89	306 (42.1)	44 (6.1)	7 (1.0)
45-59	40 (5.5)	6 (0.8)	3 (0.4)
30-44	9 (1.2)	5 (0.7)	2 (0.3)
15-29	2 (0.3)	3 (0.4)	2 (0.3)
<15	1 (0.1)	0 (0)	0 (0)

*184 patients (**25%**) at moderate to high risk of CKD progression*

Beaudin, 2019, WSS, Sept 23:5:30-7:00

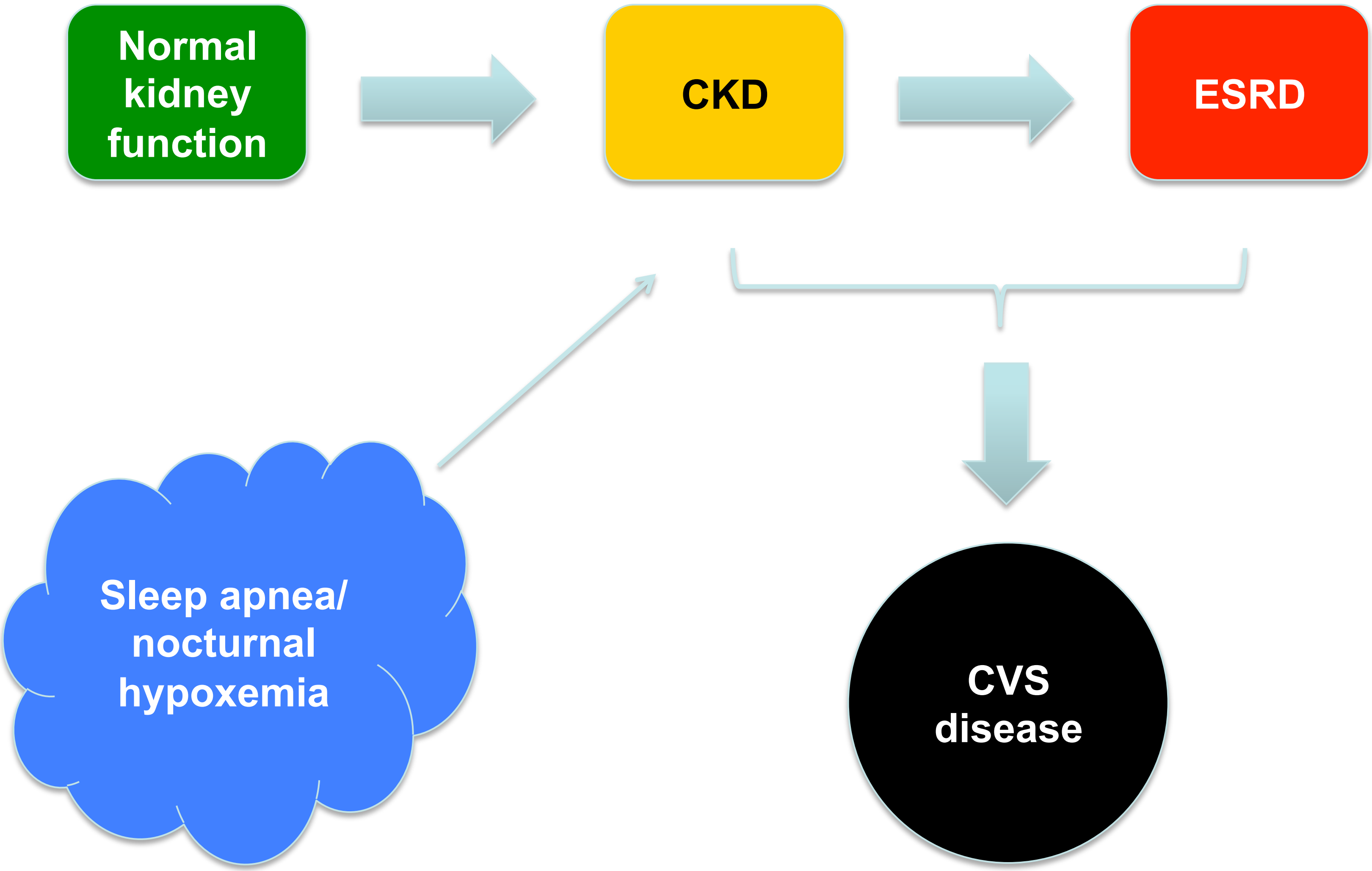
RCT: Treatment of OSA in patients with CKD:
- *Impact on kidney function*



Rimke, BMJ Open, 2019:9:e024632

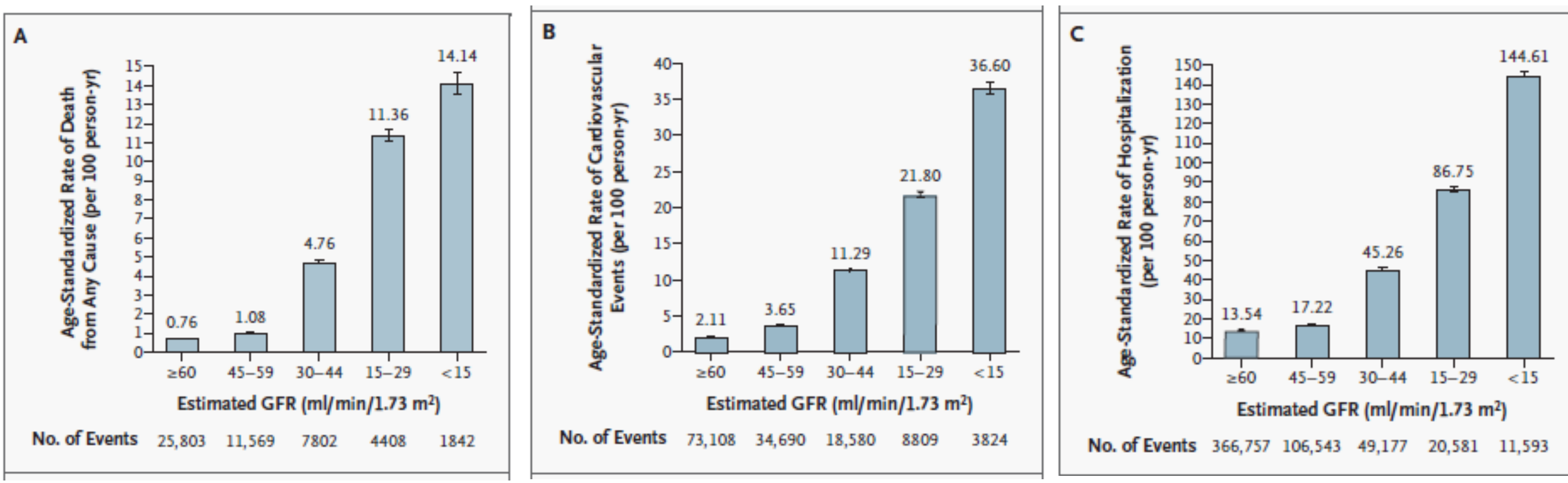
Why is this important ?

- *Impact of CKD/ESRD on CVS outcomes*



CKD associated with worse Outcomes

Death Rate | CVS Events | Hospitalizations



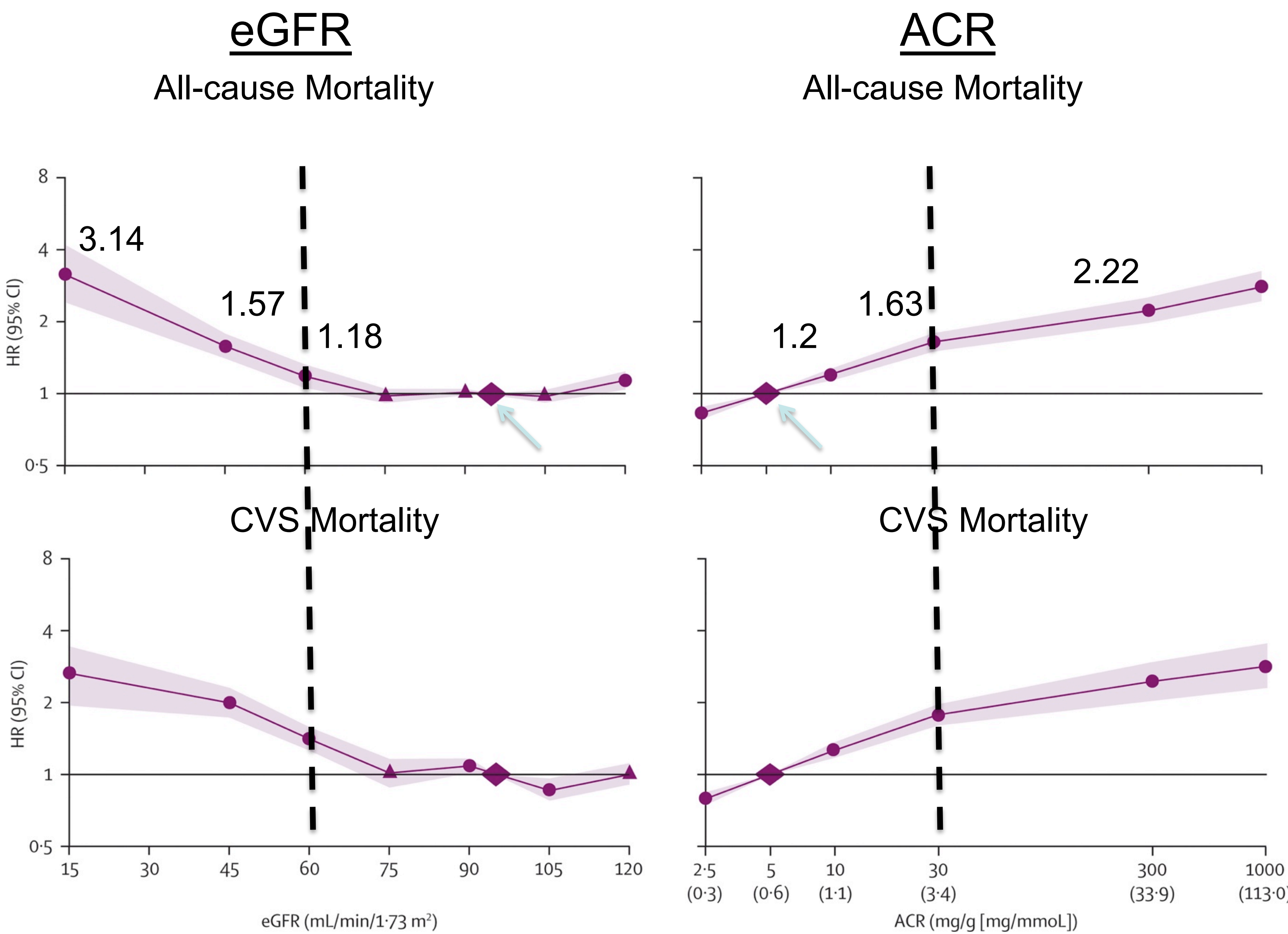
Go AS, NEJM 2004;351:1296-305

eGFR & ACR: All-Cause and CVS Mortality

- Meta-analysis, 21 gen population cohorts
  - >1000 pts, baseline eGFR and ACR/dipstick
  - Mortality (all-cause and CVS)
  - Excluded studies CVS disease or risk factors

- 14 studies with ACR: 105,872 pts
  - Median age 61 yrs
  - Median follow up 7.9 years

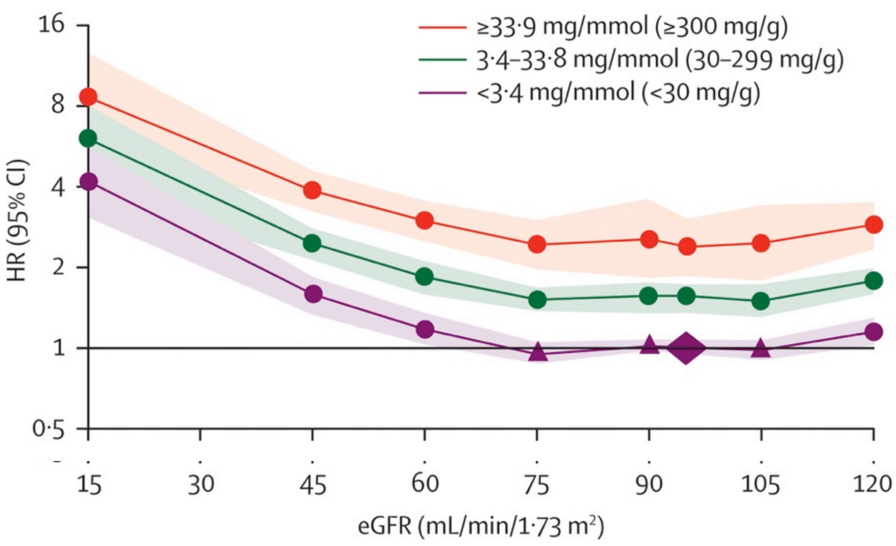
CKD Prognosis Consortium, Lancet 2010, 375:2073-81



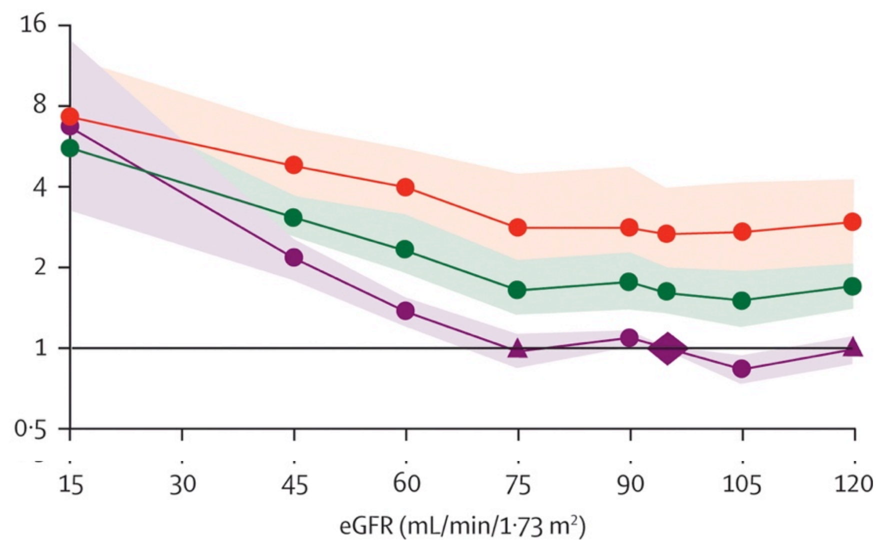
CKD Prognosis Consortium, Lancet 2010, 375:2073-81

eGFR and categorical albuminuria (ACR)

<u>All-cause Mortality</u>



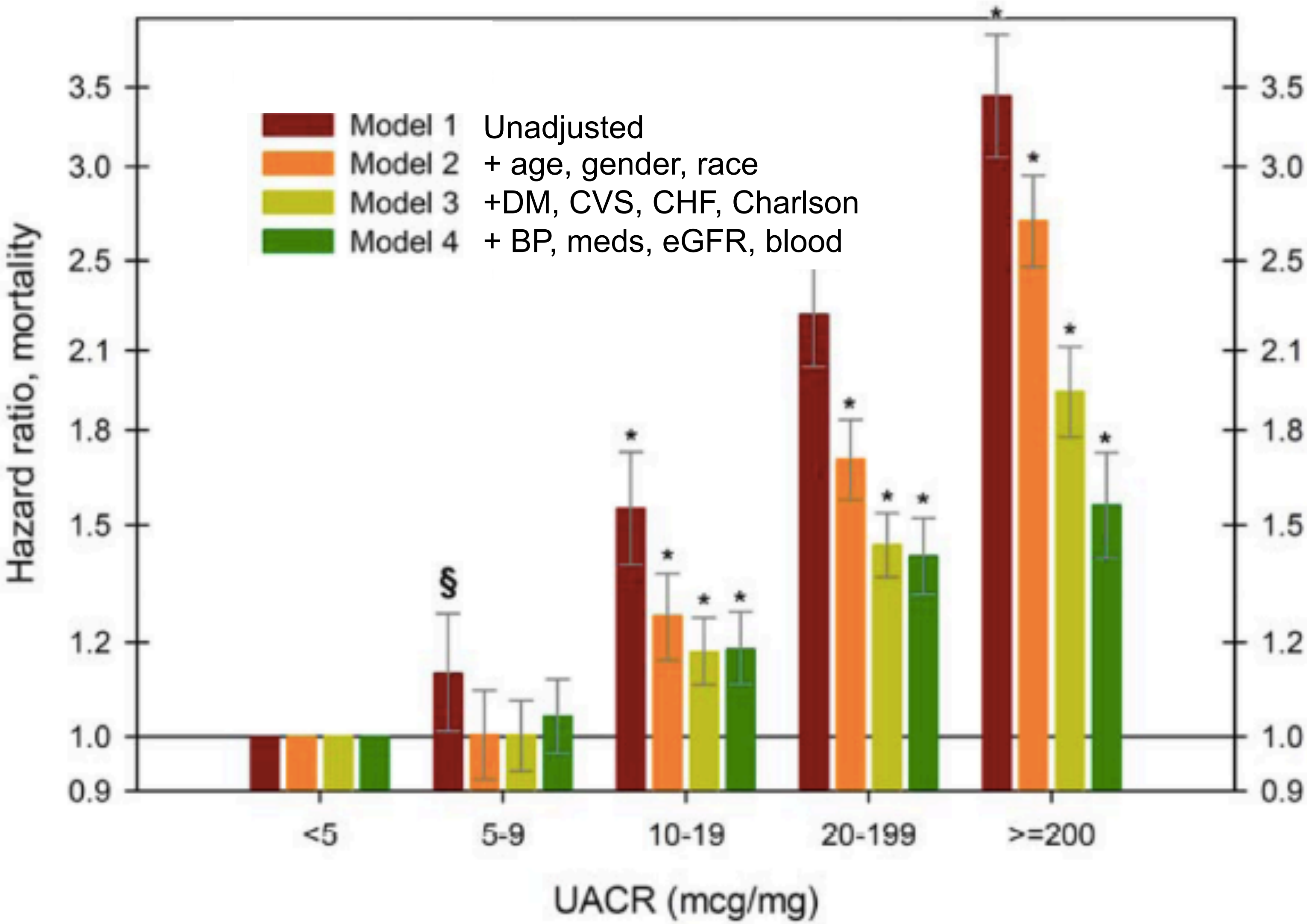
<u>CVS Mortality</u>



eGFR and albuminuria associated with mortality
- independently of each other (no evidence of interaction)
- independently of traditional CVS risk factors (excluded)

CKD Prognosis Consortium, Lancet 2010, 375:2073-81

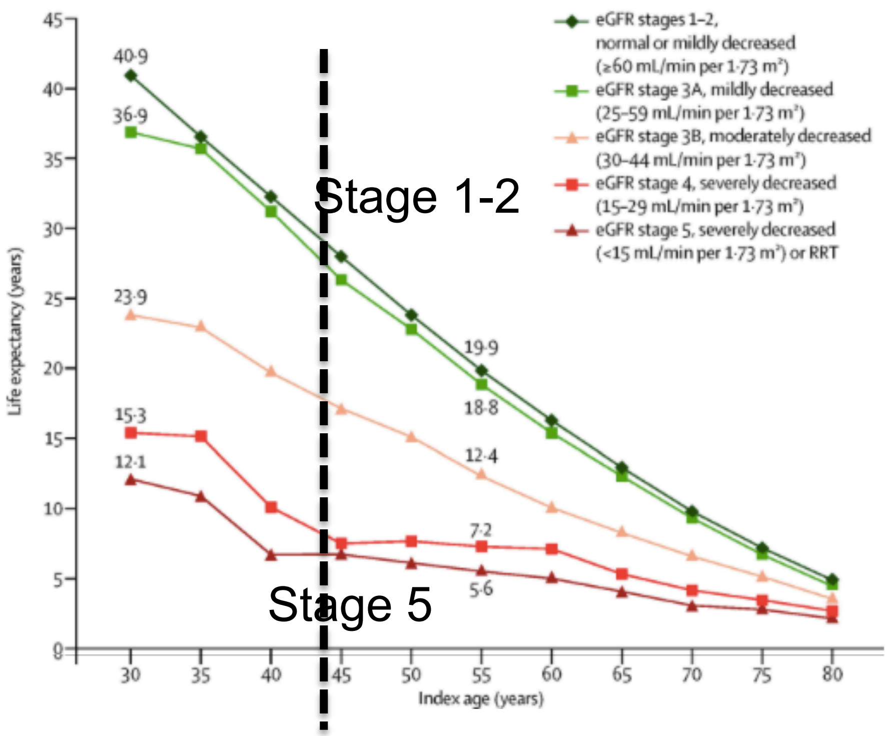
Albuminuria (UACR) and All-Cause Mortality
-Adjusted for co-morbidities



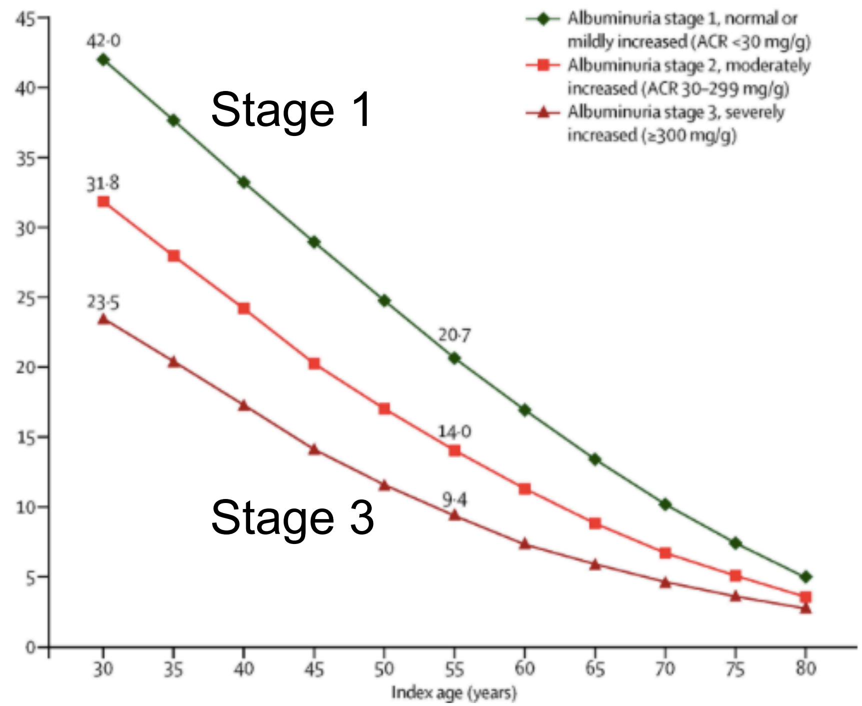
Kovesdy, J Am Coll Cardiol 2013;61:1626-33

CKD: Life expectancy per eGFR and ACR stage

eGFR stage



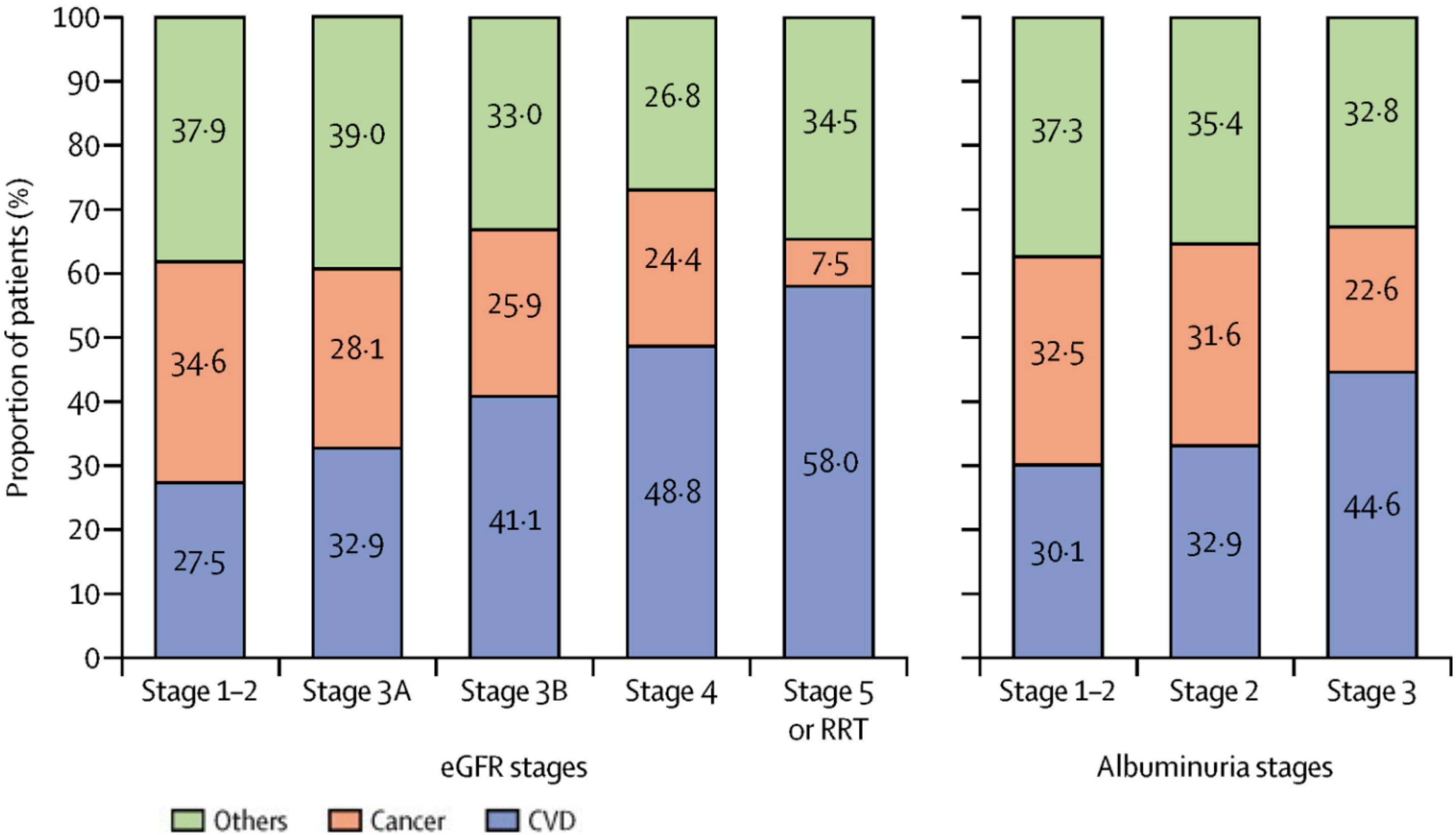
ACR stage



Dx CKD 4,5 in middle age reduces life expectancy by approx 15 yrs
Dx DM ················approx 8 yrs

Gansevoort, Lancet 2013;382:339-52

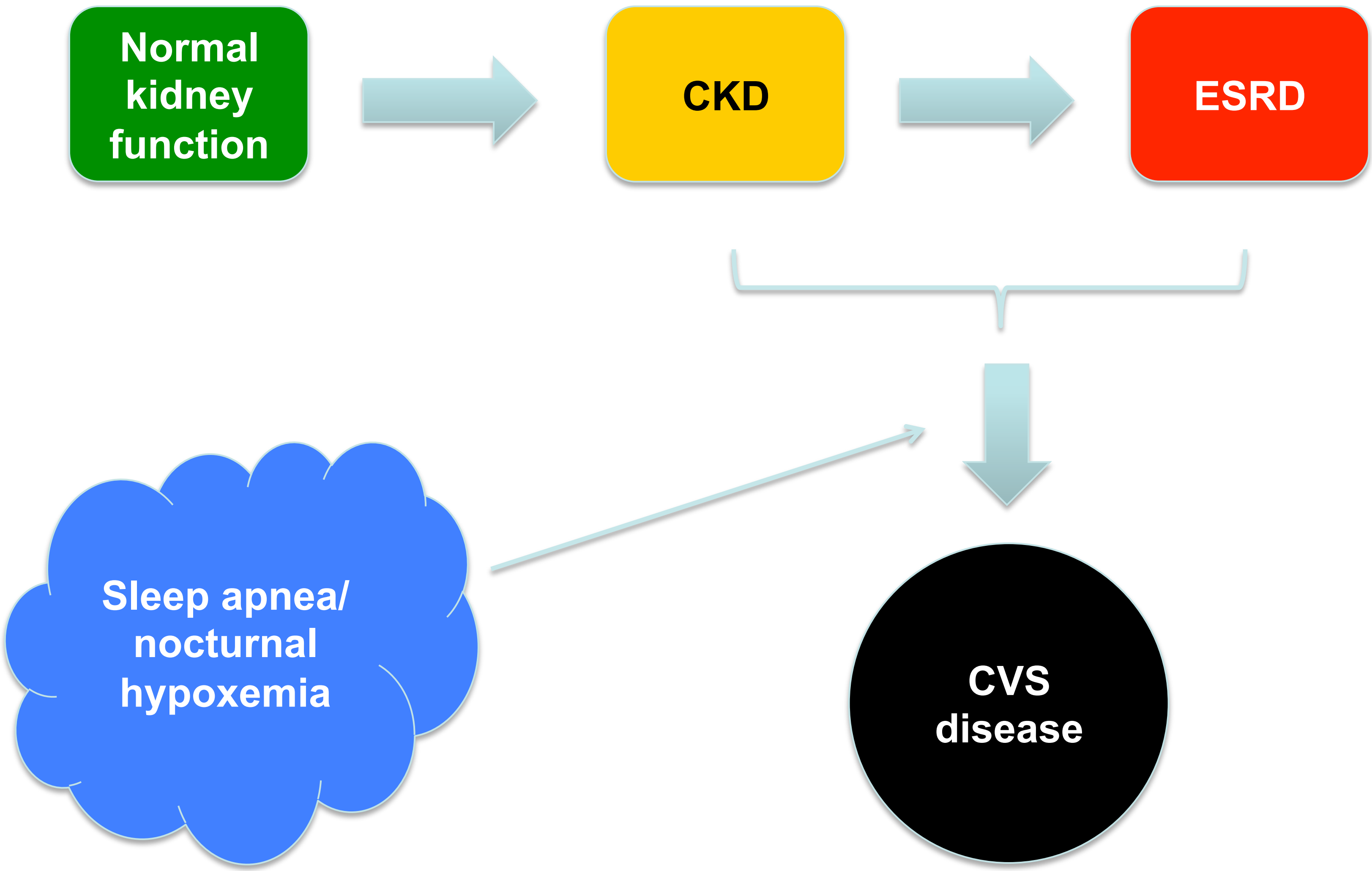
CKD: Cause of death per eGFR and ACR stage



Gansevoort, Lancet 2013;382:339-52

Why is this important ?

- *Impact of CKD/ESRD on CVS outcomes*

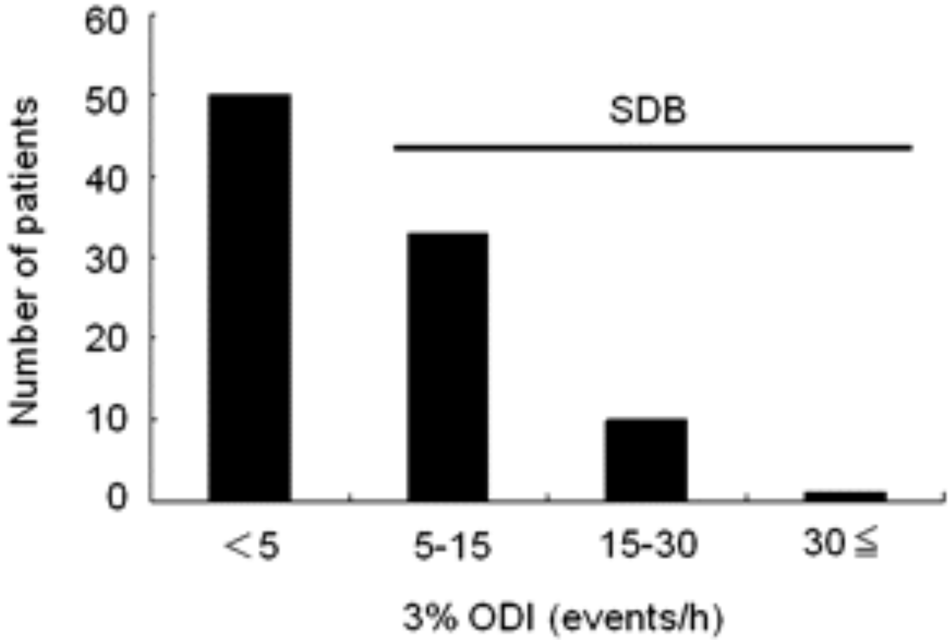


ESRD: OSA and CVS morbidity/mortality
- *Hemodialysis*

- 94 CHD pts, 64±1 yr, BMI 22±1, 53% male
- Overnight oximetry with sleep log
  - SDB: 3% ODI>5
- Primary outcome
  - First CVS event (fatal or non-fatal)
  - All cause mortality

Masuda, Nephrol Dialy Transplant 2011;26:2289-2295

ESRD: OSA and CVS morbidity/mortality
-*Nocturnal Hypoxemia*



3% ODI	*n* (%)
<5	50 (53.2)
5-15	33 (35.1)
15-30	10 (10.6)
30≦	1 (1.1)

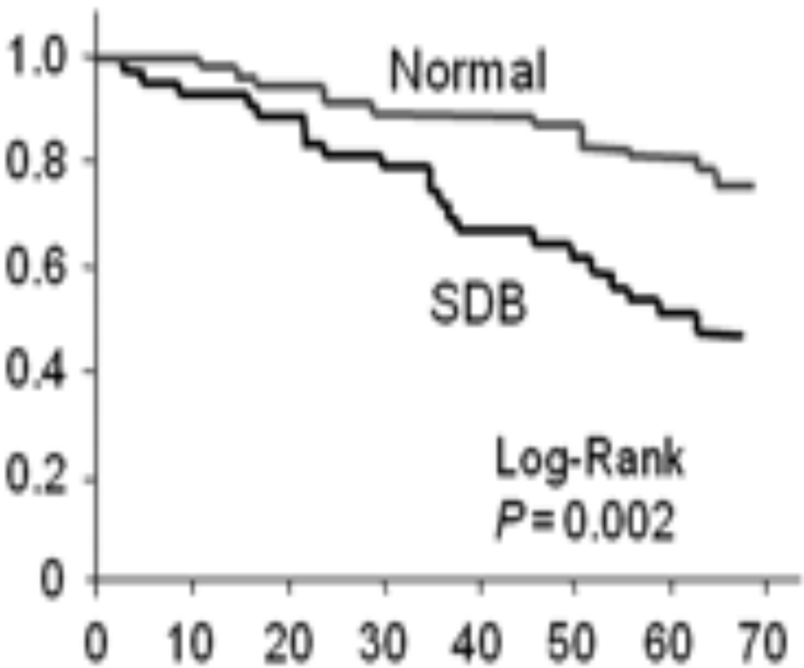
	Normal	SDB
ODI, /hr	2.0±0.2	12.3±1.3
SaO2<95%,%	6.7±2.8	27.5±3.9

Masuda, Nephrol Dialy Transplant 2011;26:2289-2295

ESRD: OSA and CVS morbidity/mortality

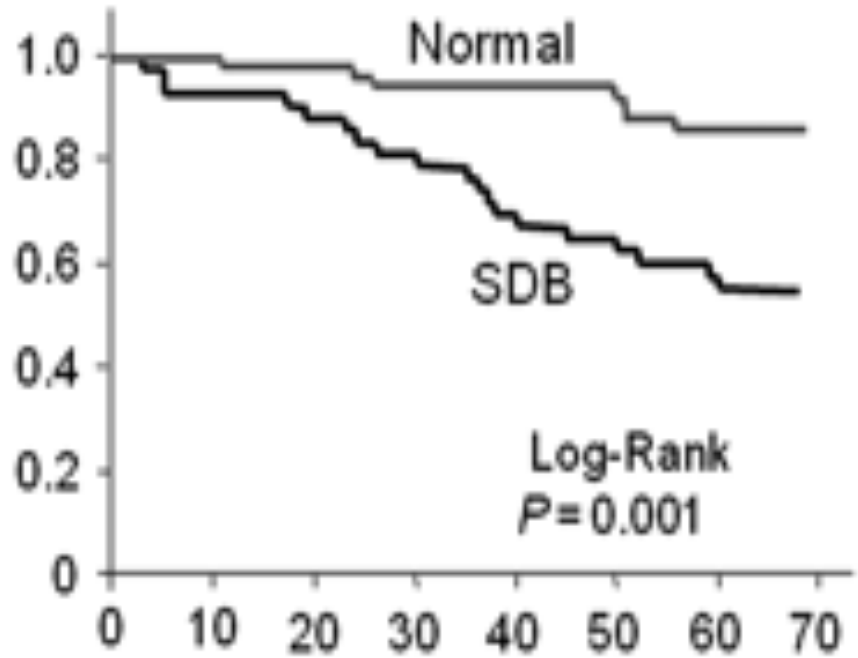
- *Median follow up 55±2 months*

CVS event free survival



Time (months)

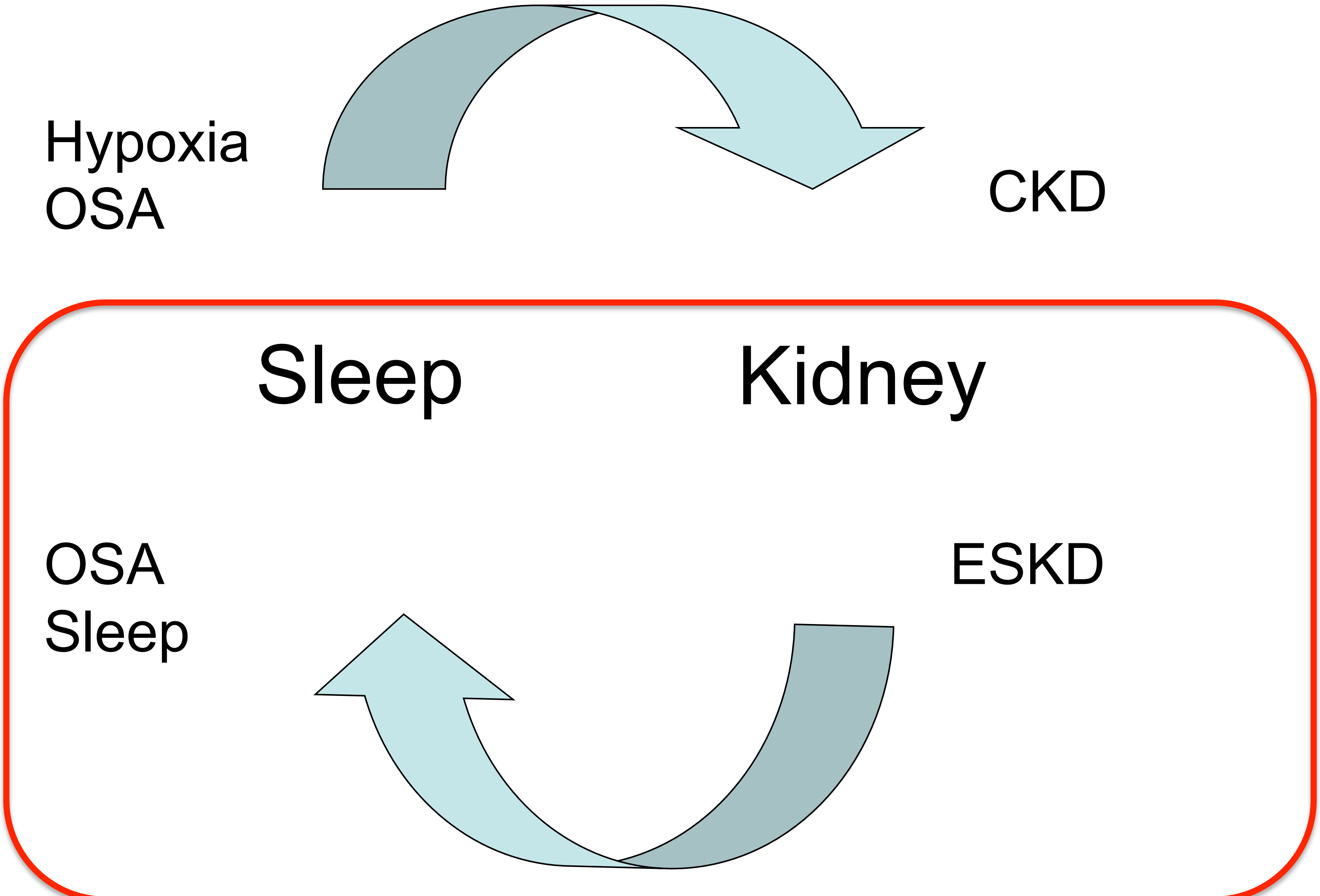
Overall survival



Time (months)

Masuda, Nephrol Dialy Transplant 2011;26:2289-2295

Sleep and Renal Function: *Bidirectional Relationship*



ESKD: Renal Replacement Therapy (RRT) - *Impact on sleep apnea*

- Standard RRT
  - Conventional hemodialysis (CHD)
  - Chronic ambulatory peritoneal dialysis (CAPD)

- Intensive RRT
  - Nocturnal hemodialysis (NHD)
  - Nocturnal peritoneal dialysis (NPD)
  - Kidney transplant

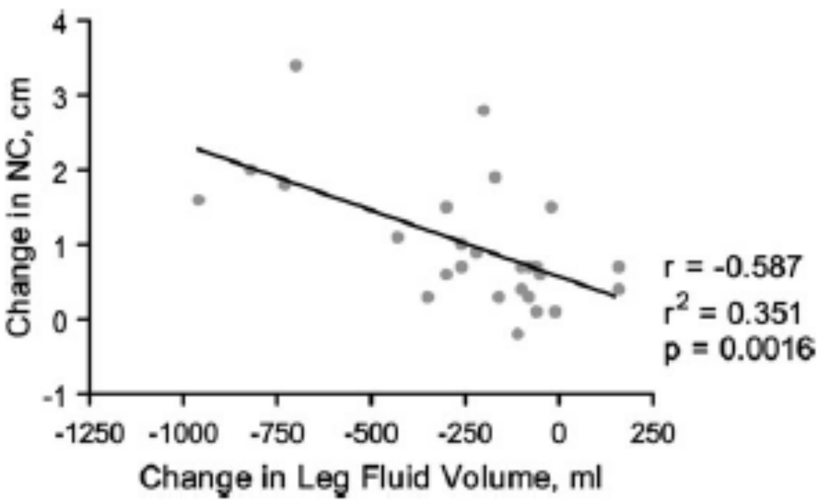
Kennedy 2018, J Nephrol;31:61-70

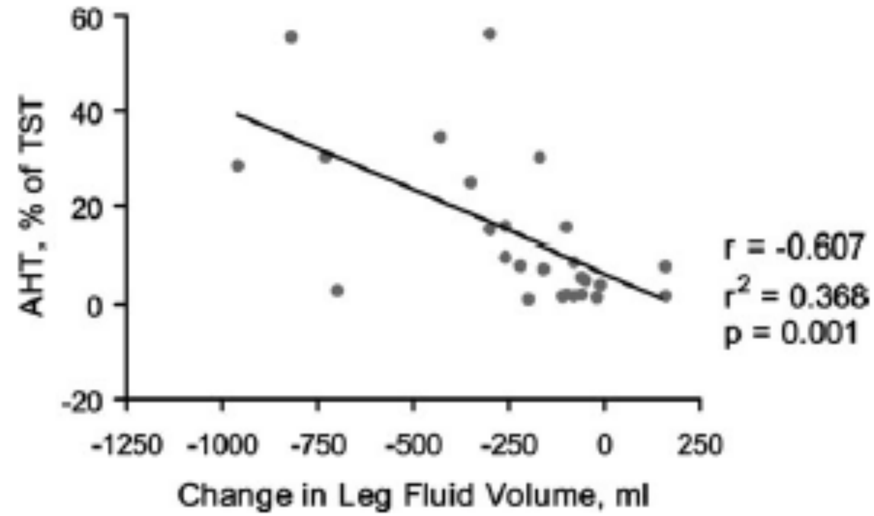
CHD: *Rostral fluid shift*

- 26 ESKD pts, CHD, 45±15 yrs, BMI 27±8
- Overnight PSG
  - AHI≥15: 12 pts (46%)
- Overnight change
  - Leg fluid volume (LFV)
  - Neck circumference (NC)

Elias 2012, Nephrol Dial Transplant;27:1569-1573

CHD: *Rostral fluid shift*

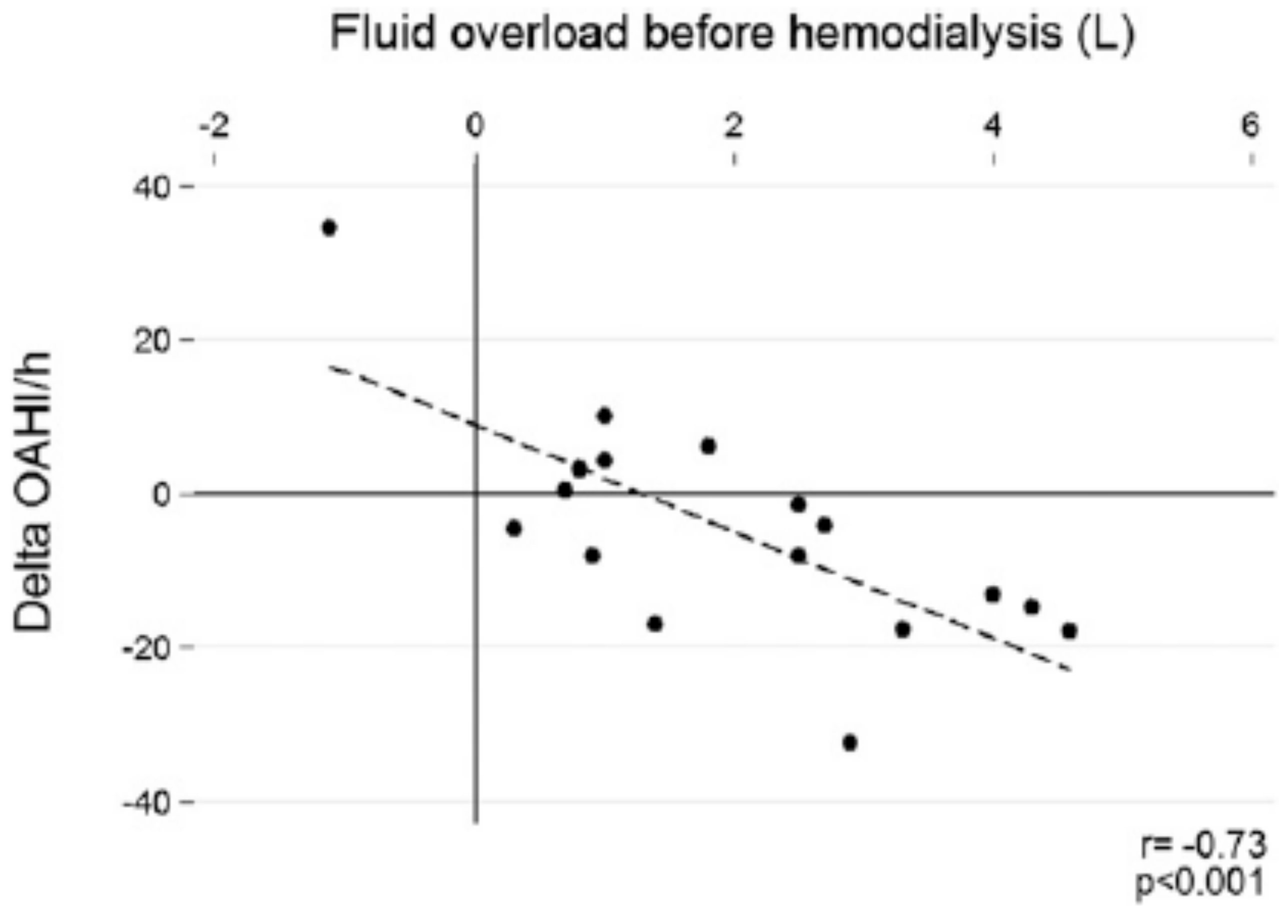




Independent variable	Correlation coefficient (*r*)	r^2	P
Male gender	0.322	0.104	0.024
Change in LFV	−0.356	0.127	0.021
Age	0.403	0.162	0.011
Total model	0.802	0.643	0.0001

Elias 2012, Nephrol Dial Transplant;27:1569-1573

CHD: Rostral fluid shift
- Dependent on fluid overload



Ogna 2015, Clin J Am Soc Nephrol;10:1002-1010

CHD: Rostral fluid shift
- Dependent on fluid overload

Factor	Multivariate Linear Regression	
	Change in OAHI (no./h) β (95% CI)	*P* Value
OAHI pre-HD (no./h)	0.3 (0.0 to 0.5)	0.05
Fluid overload pre-HD (L)	6.5 (1.6 to 11.4)	0.01
ΔFluid overload (L)	2.1 (−5.1 to 9.2)	0.54
ΔNocturnal rostral fluid shift (L)	3.1 (−15.3 to 21.6)	0.72

Fluid overload pre-hemodialysis strongest predictor of reduction in AHI following CHD

Ogna 2015, Clin J Am Soc Nephrol;10:1002-1010

CHD: *Ultrafiltration*

- 15 pts, CHD, 54±10 yrs, BMI 25±5

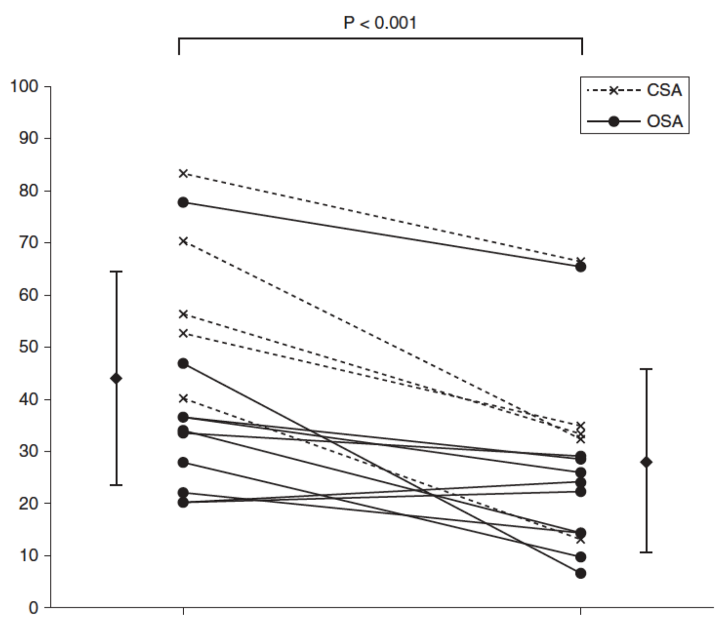
- PSG: AHI 44±20; 10 OSA, 5 CSA
- Bioelectrical impedance: ECFV

- Ultrafiltration without dialysis
  - 2.17±0.45 L removed
  - No change in urea

Lyons 2015, Am J Respir Crit Care Med;11:1287-1294

CHD: *Ultrafiltration(UF)*

<u>Change in AHI</u>

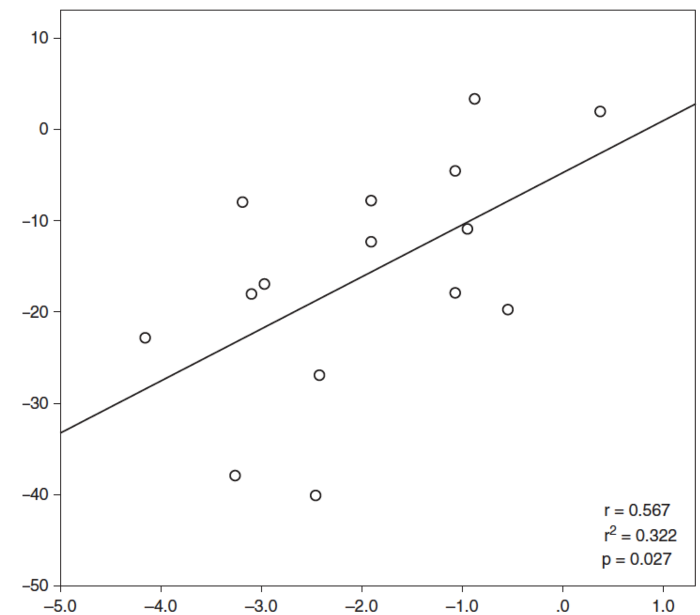


Baseline
44±20

Post UF
28±18

<u>Correlation ΔECFV and ΔAHI</u>

ΔAHI post UF



ΔECFV post UF)

Lyons 2015, Am J Respir Crit Care Med;11:1287-1294

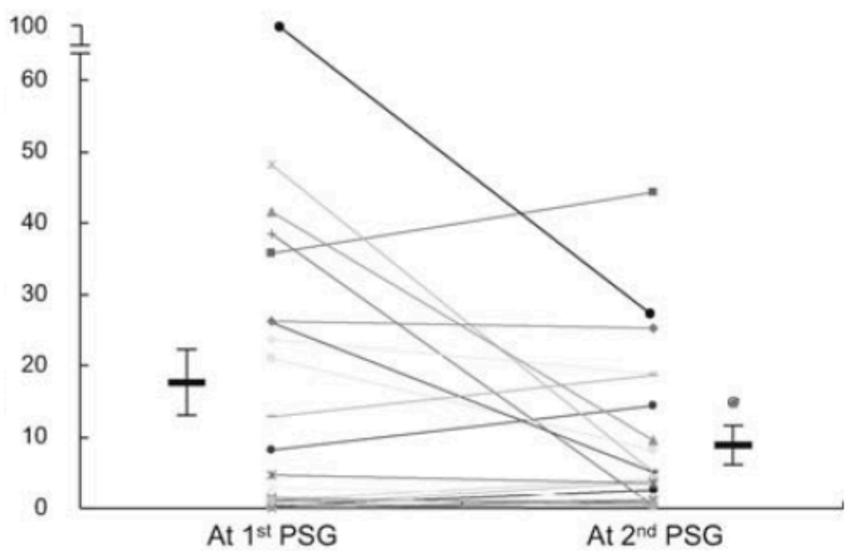
Nephrotic syndrome: *Rostral fluid shift*

- 23 pts, 45±19 yrs, BMI 25±6, eGFR 94±45
- Proteinuria, hypo-albuminemia, leg edema
  - Steroid responsive
  - Hydration fraction (TBW, % body wt) fell 14±12%
- Baseline PSG: 11 pts had OSA (RDI 35±8)
- Follow up PSG 8.1±2.6 mths later

Tang 2012, Nephrol Dial Transplant;27:2788-2794

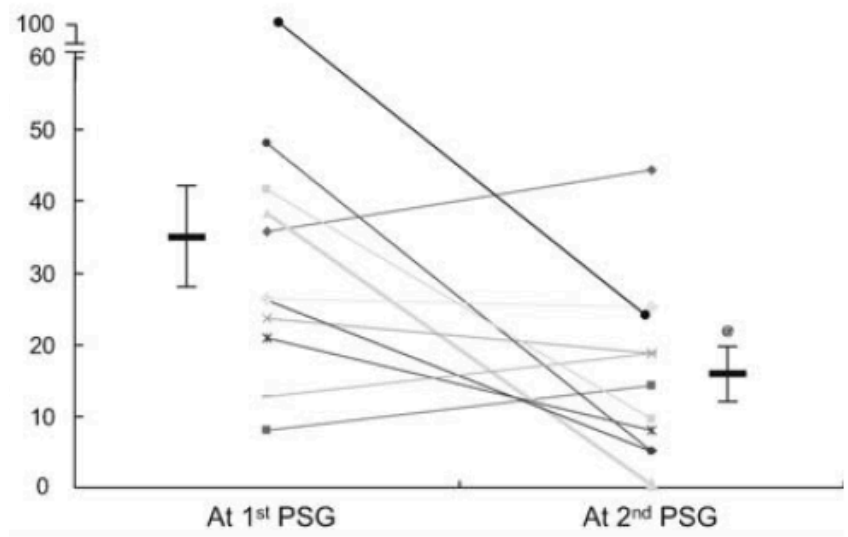
Nephrotic syndrome: *Rostral fluid shift*

RDI (all patients)



17± 5 9±3

RDI (patients with OSA)



35±8 17±4

Tang 2012, Nephrol Dial Transplant;27:2788-2794

ESRD: Renal Replacement Therapy (RRT) - *Impact on sleep apnea*

- Standard RRT
  - – Conventional hemodialysis (CHD)
  - – Chronic ambulatory peritoneal dialysis (CAPD)

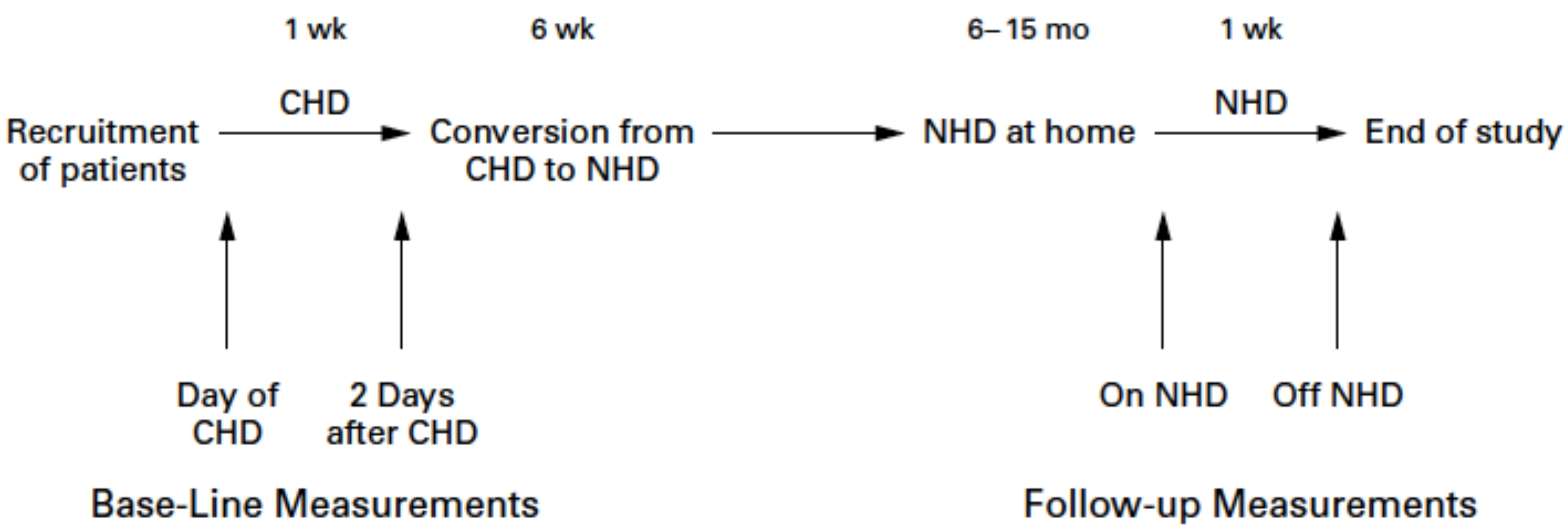
- Intensive RRT
  - – Nocturnal hemodialysis (NHD)
  - – Nocturnal peritoneal dialysis (NPD)
  - – Kidney transplant

Kennedy 2018, J Nephrol;31:61-70

Nocturnal hemodialysis (NHD) vs CHD

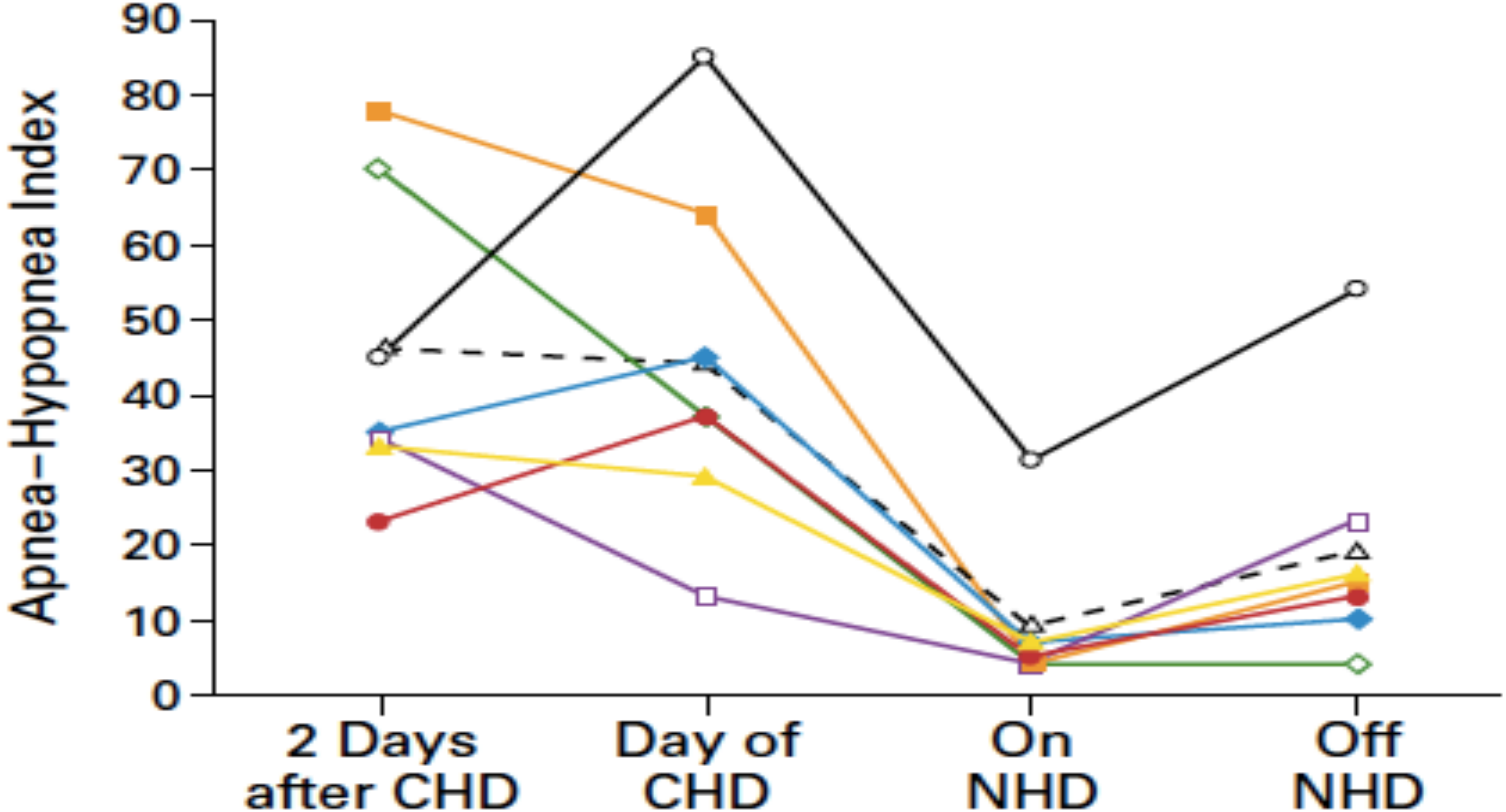
14 pts, CHD, 45±9 yrs, BMI 26±6

- OSA (7 pts), CSA (1 pt)



Hanly 2001, N Engl J Med; 344:102-107

Nocturnal hemodialysis (NHD) vs CHD



Hanly 2001, N Engl J Med; 344:102-107

ESRD/OSA: *Ventilatory instability*

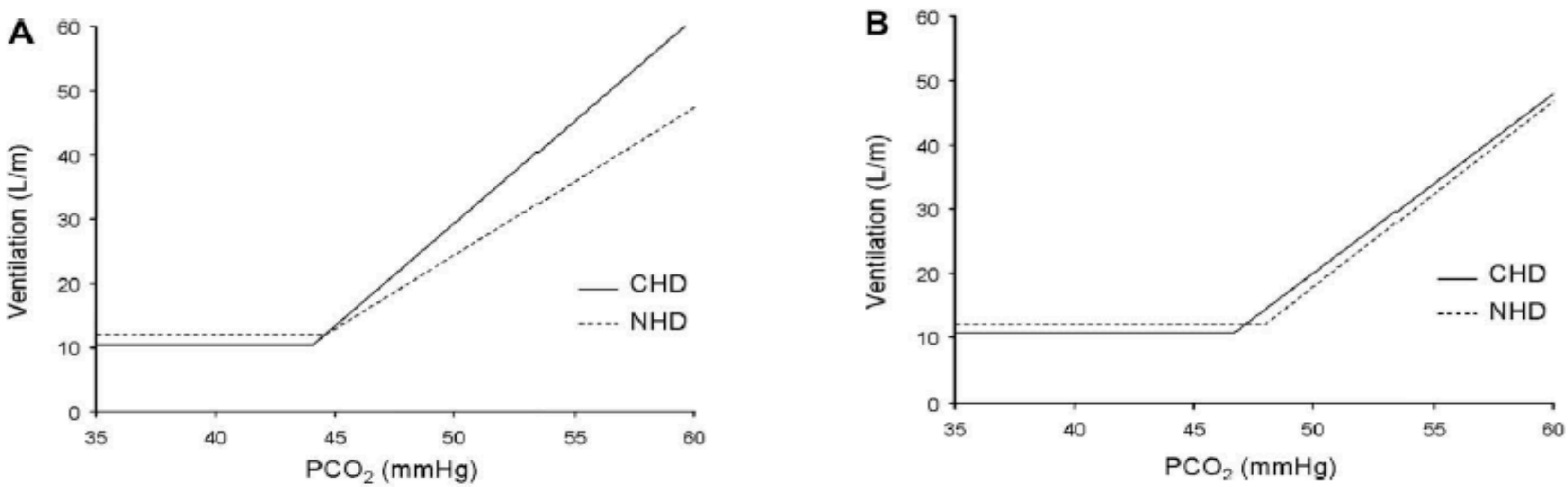
- 24 pts, CHD, 31-68 yrs
  - PSG: Apneic (AHI≥15) vs non-apneic (AHI<15)
- CHD converted to NHD
  - Apneic "responders": AHI fell>50% and/or <15
  - Apneic "non-responder"
- Ventilatory response to hypercapnia
  - Modified Read rebreathing technique

Beecroft 2009, Sleep Medicine;10:47-54

Ventilatory response to Hypercapnia
-*Apneic responders vs non-responders*

Responders
AHI: 43±20 to 10±7

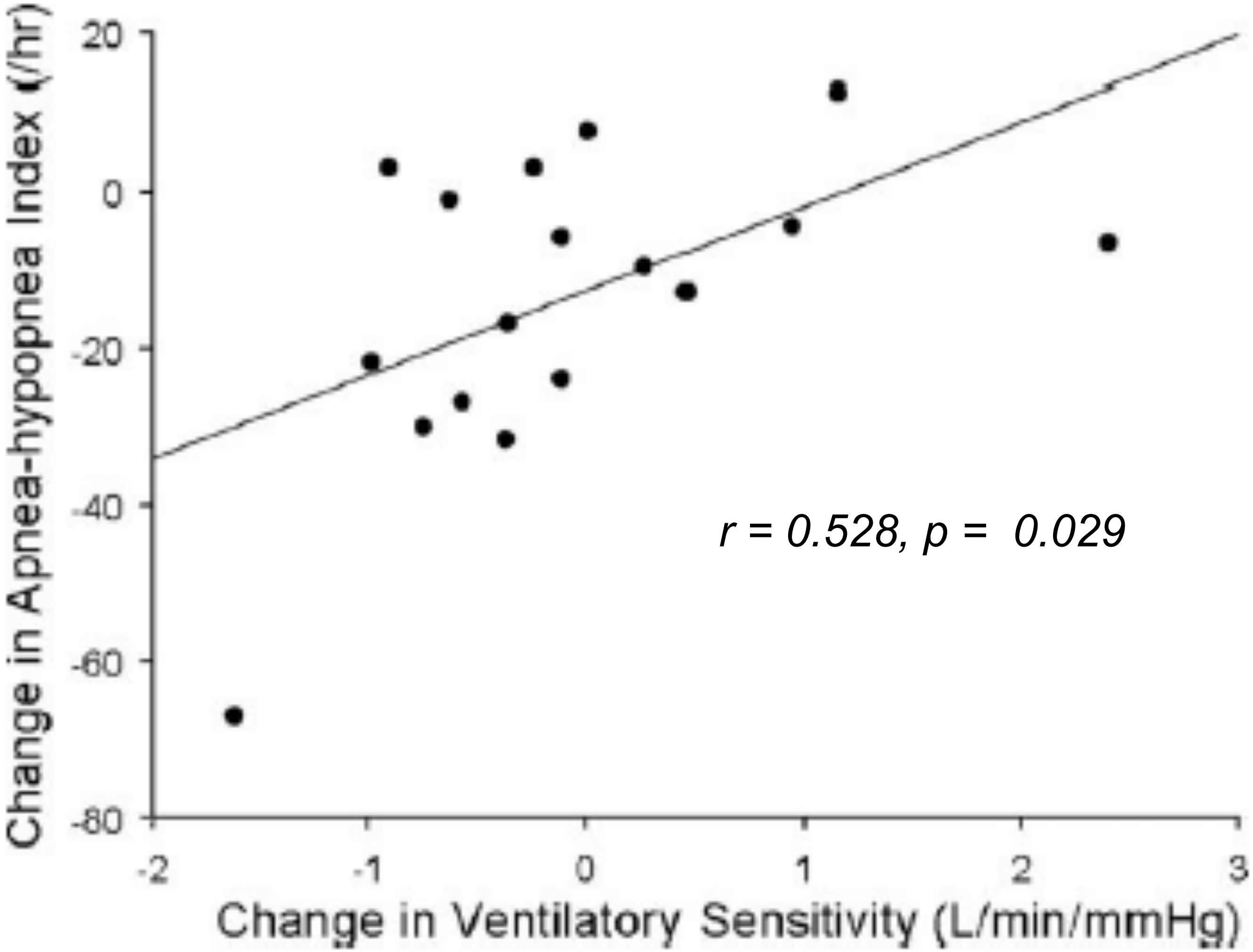
Non-responders
AHI: 39±21 to 31±11



Ventilatory sensitivity to hypercapnia reduced following conversion from CHD to NHD in apneic responders

Beecroft 2009, Sleep Medicine;10:47-54

Change in ventilatory sensitivity
-Correlated with change in AHI



Beecroft 2009, Sleep Medicine;10:47-54

NHD reduced ventilatory sensitivity - *Potential mechanisms*

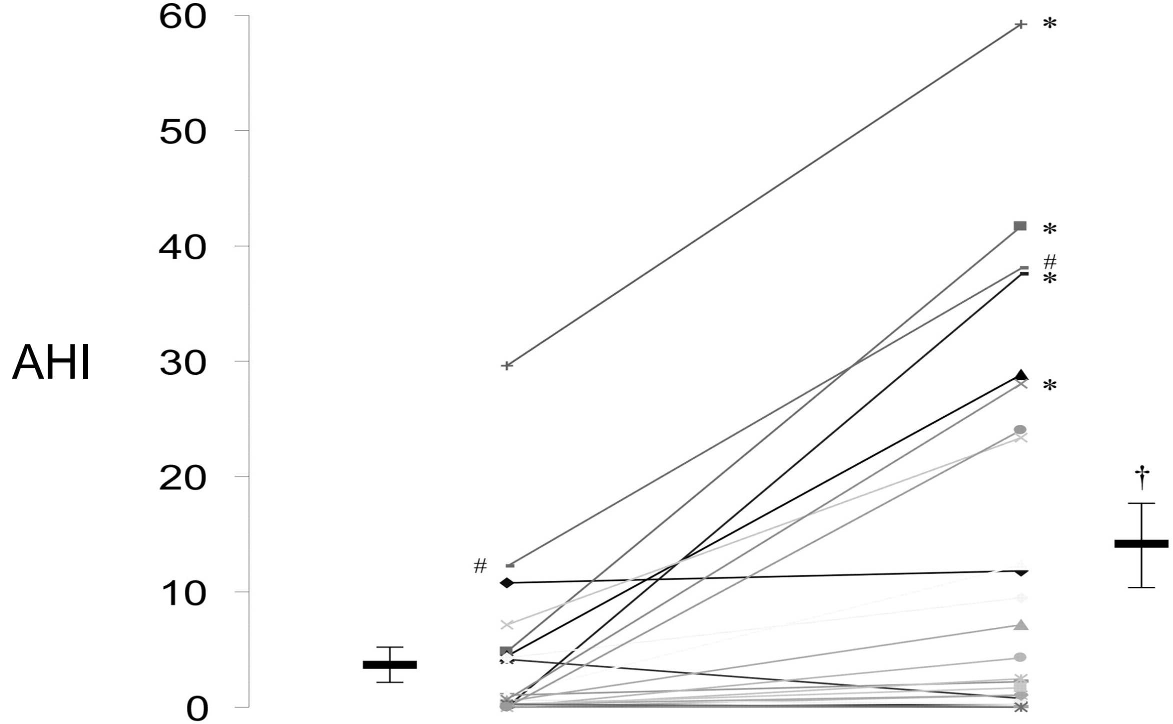
- Uremia
  - Better clearance of toxins, middle molecules
- Sympathetic nervous system activation
  - Reduced by NHD
- Ultrafiltration
  - Resolution of interstitial pulmonary edema

Nocturnal Peritoneal Dialysis (NPD) vs CAPD

- 24 ESKD pts, 51±13 yrs, BMI 21±4
  - Cycler-assisted NPD (8 wks) vs CAPD
- PSG on NPD vs CAPD
- Bioelectrical impedance analysis
  - Change in hydration fraction (HF=TBW, % wt)

Tang 2006, J Am Soc Nephrol;17:2607-2616

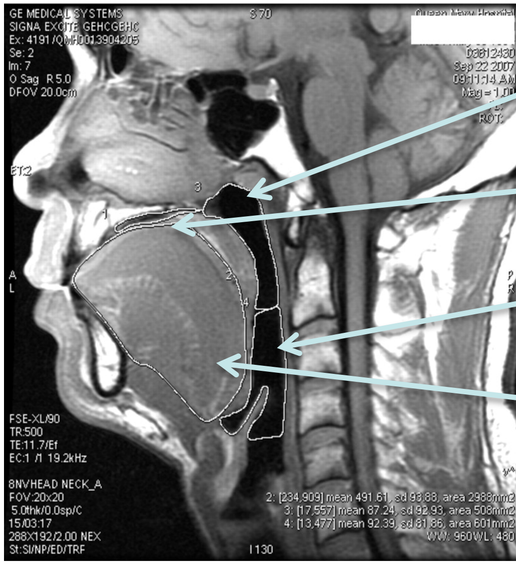
Nocturnal Peritoneal Dialysis (NPD) vs CAPD



	NPD	CAPD
AHI	3.4±1.3	14±4
HF	-3.6±0.6	-0.7±0.5

Tang 2006, J Am Soc Nephrol;17:2607-2616

Nocturnal Peritoneal Dialysis (NPD) vs CAPD



Nasopharynx (NP)

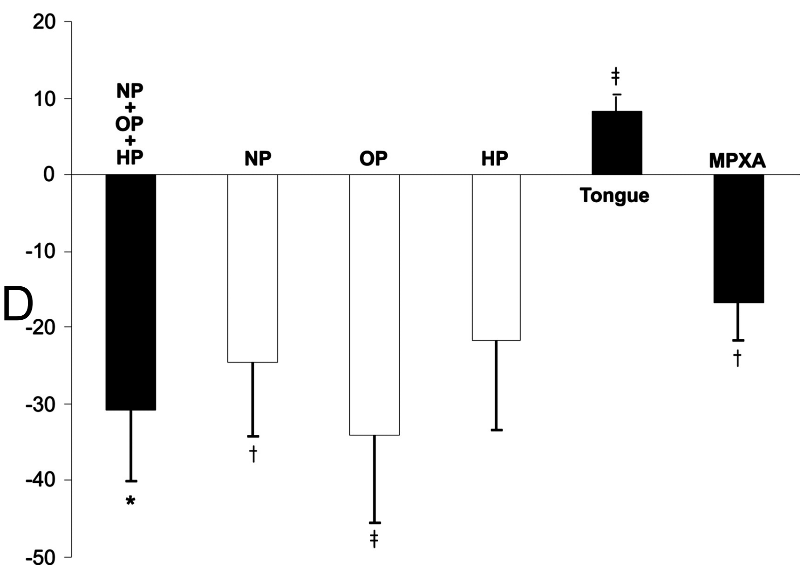
Oropharynx (OP)

Hypopharynx (HP)

Tongue

MPXA

% Volumetric change after conversion to CAPD



Reduction in volume ≈ Δ AHI (r=-0.565, p=0.035)

Tang 2009, Clin J Am Soc Nephrol;4:410-418

Kidney Transplantation

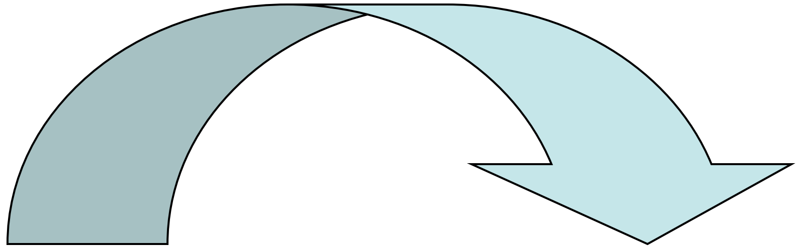
Reference	All n	Apneic n	AHI Pre TP	AHI Post TP	Comments
Jurado-Gamez 2008	9	3	10±11	4.9±6.1	
Beecroft 2009	18	11	20±15	24±21	27% "responders"*
Rodrigues 2010	34	9	5.3±7.3	3.1±4.5	
Lee 2011	20	12	13.5 (2-40)	4.5 (0-20)	66% "responders"

* Responder = AHI reduced>50% and/or AHI<10/hr

- No consistent benefit
  - Heterogenous group
    - Pre-existing SDB not related to ESKD
    - New risk factors for SDB post TP eg weight gain
- No mechanistic studies
  - Phenotype

Implications for Management

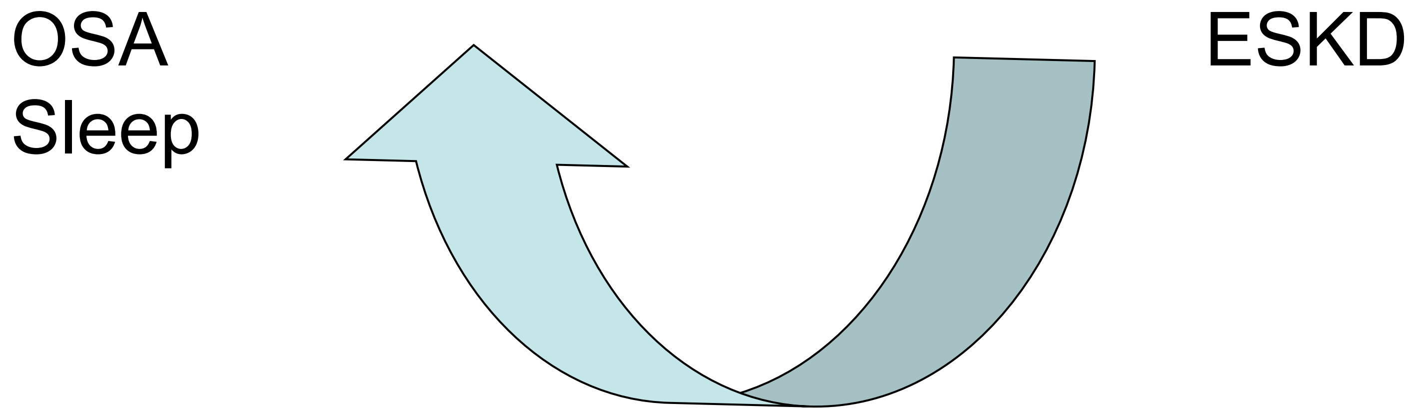
Hypoxia
OSA



CKD

- Consider whether un-recognized OSA is contributing to symptoms
  - *Overlapping symptoms*
- Awareness of *potential* for OSA/hypoxemia to injure the kidney
  - *Benefit of OSA treatment to kidney function not established*
- Consider treatment of OSA/hypoxemia in specific phenotypes
  - *Resistant hypertension in patient with co-existing CKD*
  - *Accelerated decline in kidney function despite conventional CKD Tx*

Implications for Management



•Optimize correction of volume overload
  •*Predominant mechanism for pathogenesis of OSA in ESKD*

•Consider CPAP trial in symptomatic patient
  •*May require management of co-existing insomnia, RLS*

•Intensification of RRT does not guarantee correction of OSA
  •*Clinical and objective monitoring follow up required*

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Sleep Research Program