Hypertension and sleep apnea in CKD stage 5

KDIGO Controversies Conference:
Blood Pressure in Chronic Kidney Disease

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Objectives

- To review the mechanisms of sleep apnea in ESRD
- To outline clinical implications of sympathetic over-activity
- To review the interactions between salt/ volume overload and sympathetic over-activity
- To determine potential management implications in the ESRD patient population

Sleep Apnea

- ESRD patients – but prevalence is highly variable
  - General population (2-4%)
  - ESRD (up to 50% → dependent on the "methods of ascertainment")
  - Over-representation of obstructive and central sleep apnea
- SNS over-activity → classical/important contributor of cardiovascular morbid events
- Salt + volume overload → critical pathogenetic element of sleep apnea in ESRD

Sleep Apnea with Intermittent Hemodialysis: Time for a Wake-Up Call!

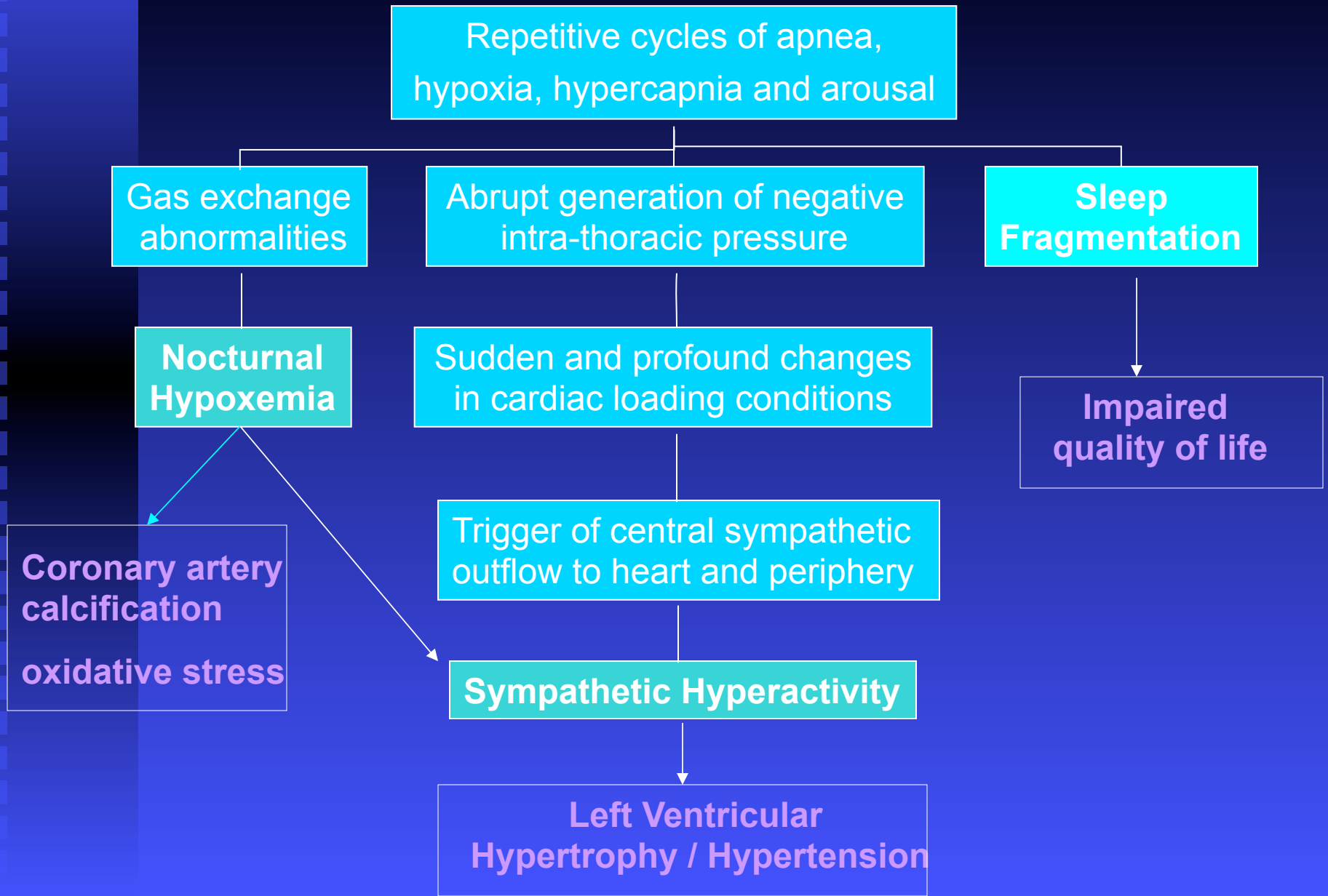
Table 2. Sleep parameters of HD and population control samples[a]

Variable	HD Population (n = 46)	Matched Controls (n = 137)	P[b]
Sleep time (min)	319.5 ± 106.3	378.9 ± 67.3	<0.001
Sleep efficiency (sleep time/total time in bed)	78.1 ± 15.3	81.3 ± 10.4	NS
Stage 1 sleep (%)[c]	5.0 ± 3.4	5.5 ± 3.65	NS
Stage 2 sleep (%)	57.6 ± 14.3	58.4 ± 11.5	NS
Stage 3 to 4 sleep (%)[c]	23.4 ± 12.2	14.3 ± 10.7	<0.001
REM sleep (%)	13.6 ± 8.2	21.7 ± 6.2	<0.001
Arousal index (arousals/h)[d]	25.1 ± 14.6	17.1 ± 8.0	<0.001
Respiratory disturbance index[d]	27.2 ± 19.3	15.2 ± 14.9	<0.001
Hypoxemic index[d,e]	7.2 ± 20.8	1.84 ± 8.4	<0.001
Lowest oxygen saturation, NREM[c]	83.6 ± 7.1	86.7 ± 5.3	<0.01
Lowest oxygen saturation, REM[c]	81.2 ± 9.7	85.9 ± 6.4	<0.001
Epworth Sleepiness Scale	9.0 ± 4.7	8.0 ± 4.3	NS

[a]Data are means ± SD. NREM, non–rapid eye movement; REM, rapid eye movement.
[b]NS = $P > 0.05$.
[c]Log-log transformation used for test of group differences.
[d]Log transformation used for test of group differences.
[e]The percentage of total sleep time with an oxygen saturation of <90%.

Unruh – JASN 2007

“Classical Model” - Sleep Apnea

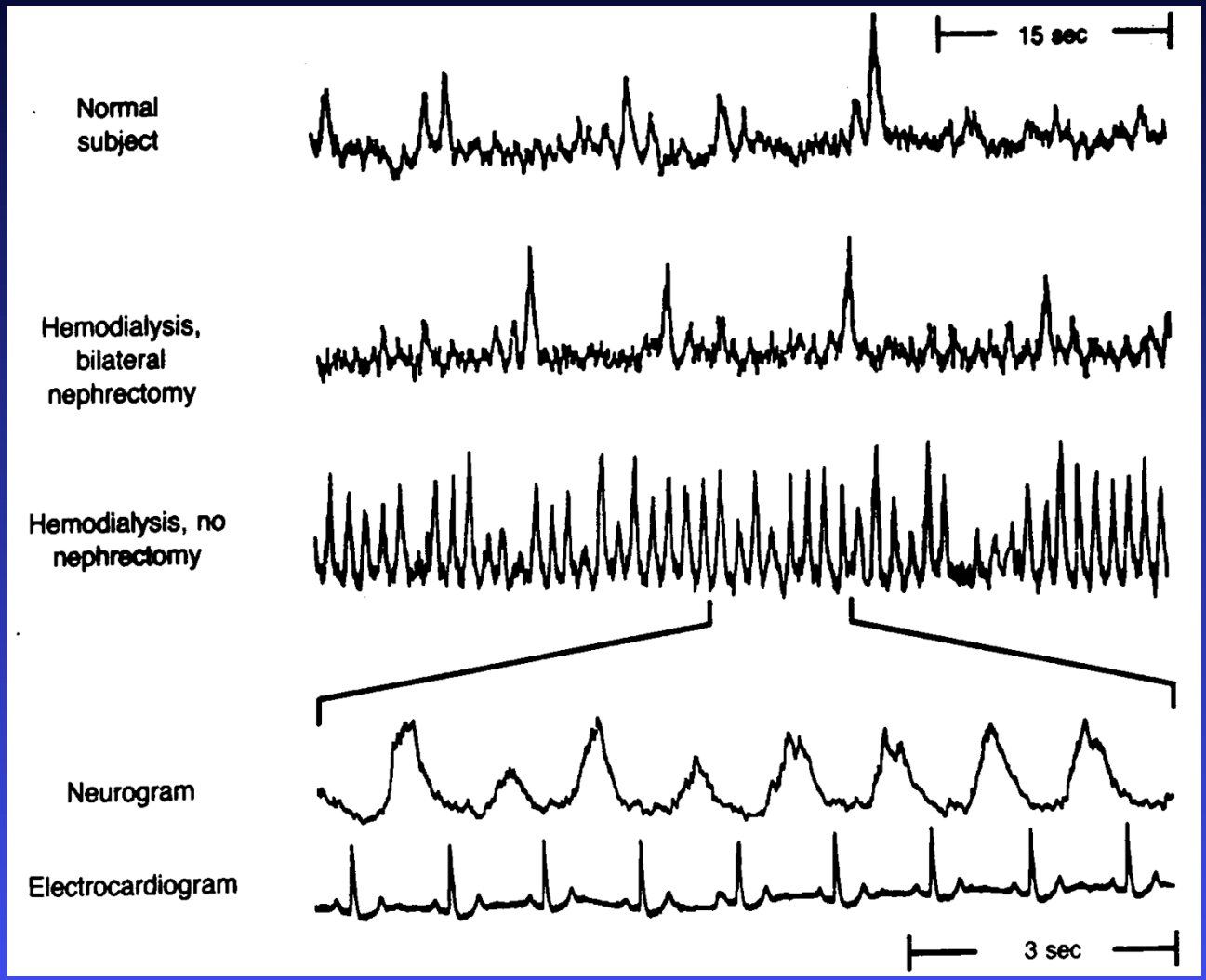


SNS over-activity → Hypertension
Cardiac Failure
Sudden Cardiac Death

Mechanisms of SNS over-activity

- Renal (Inc. production)
  - Sympathetic nerve traffic is increased
  - BUT → renal transplantation does not correct elevated MSNA
- Renal (Dec. elimination)
  - Dec. clearance
  - Recall – t1/2 is short
  - Simply increasing clearance will not be sufficient

Sympathetic over-activity in ESRD



Converse et al, NEJM 1993

Adrenergic modulation → cardiac apoptosis

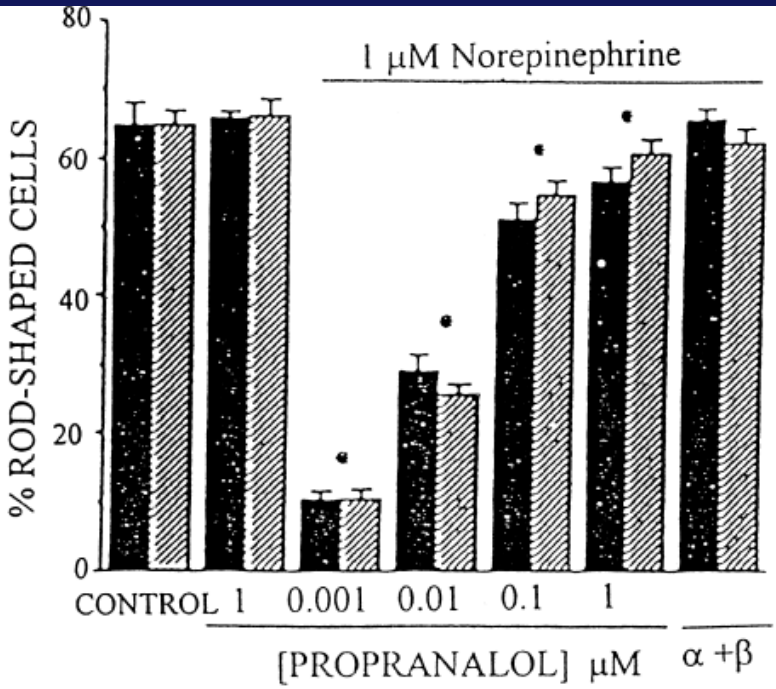


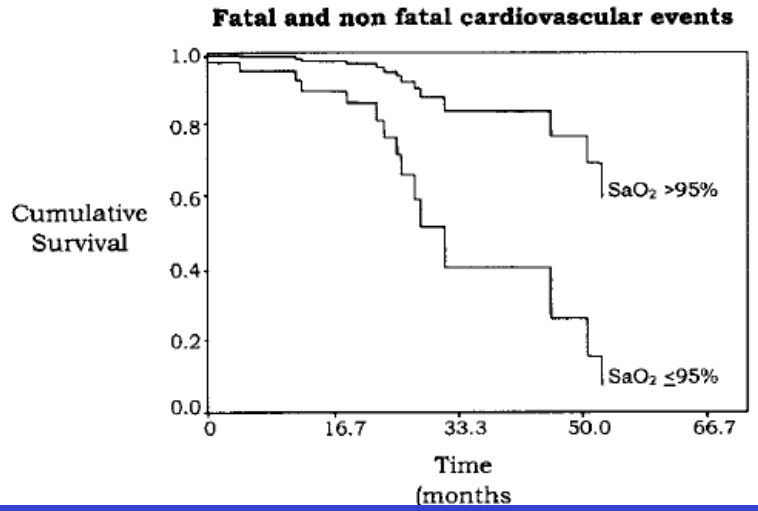
Fig. 1. Norepinephrine (1 μM) decreased the viability of adult cardiac myocytes in culture for 48 (black bars) or 72 h (hatched bars). The toxic effect was fully inhibited by the β-AR antagonist propranolol in a dose-dependent manner. Likewise, propranolol plus the α-adrenergic antagonist phentolamine (10 μM) completely blocked the effect of norepinephrine. From Mann et al. [12] with permission. (* $P<0.05$ vs. control).

Nocturnal Hypoxemia Predicts Incident Cardiovascular Complications in Dialysis Patients

CARMINE ZOCCALI, FRANCESCA MALLAMACI, and GIOVANNI TRIPEPI
CNR, Centre of Clinical Physiology and Division of Nephrology, Ospedali Riuniti, Reggio Calabria, Italy.

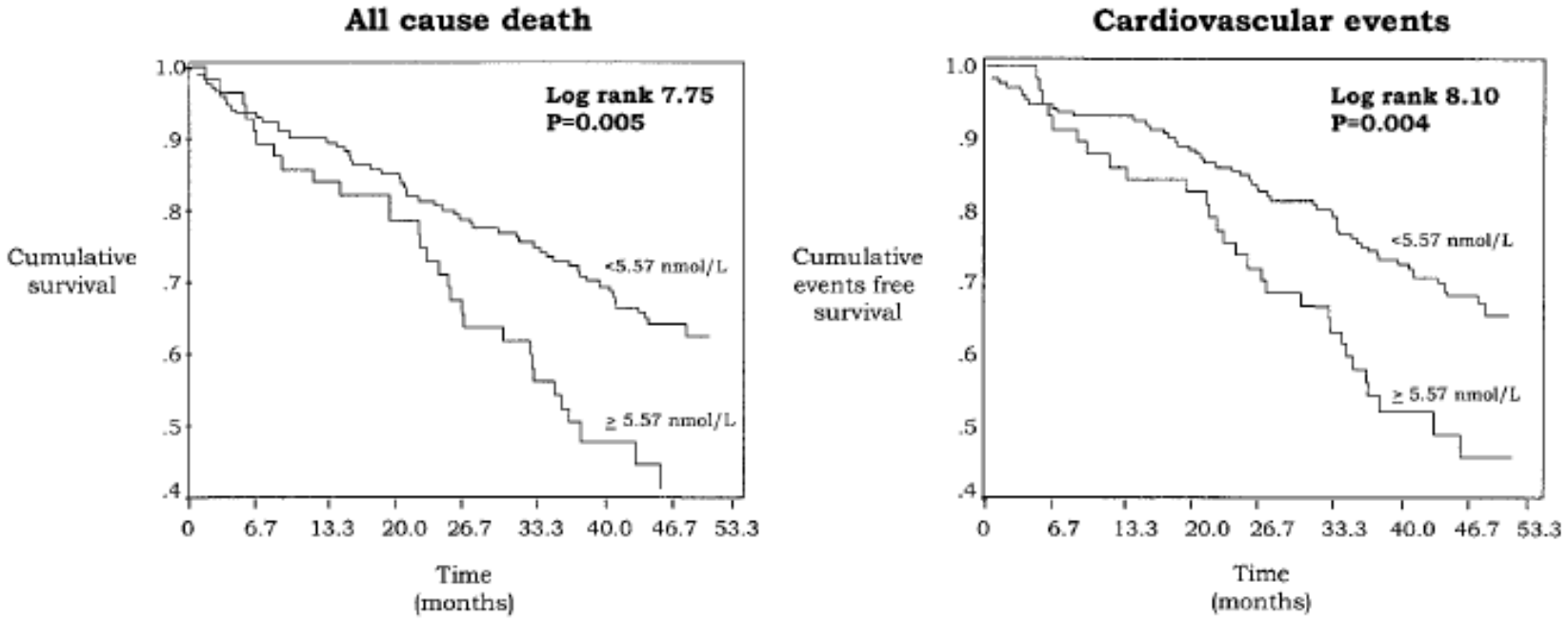
Table 4. Multivariate predictors of fatal and nonfatal cardiovascular events

Parameter	Units of Increase	Hazard Ratio (95% CI)	*P*
Age	1 yr	1.07 (1.02 to 1.13)	0.007
Average nocturnal SaO_2	1%	0.77 (0.62 to 0.95)	0.01
Cholesterol	1 mmol/L	0.49 (0.25 to 0.97)	0.04



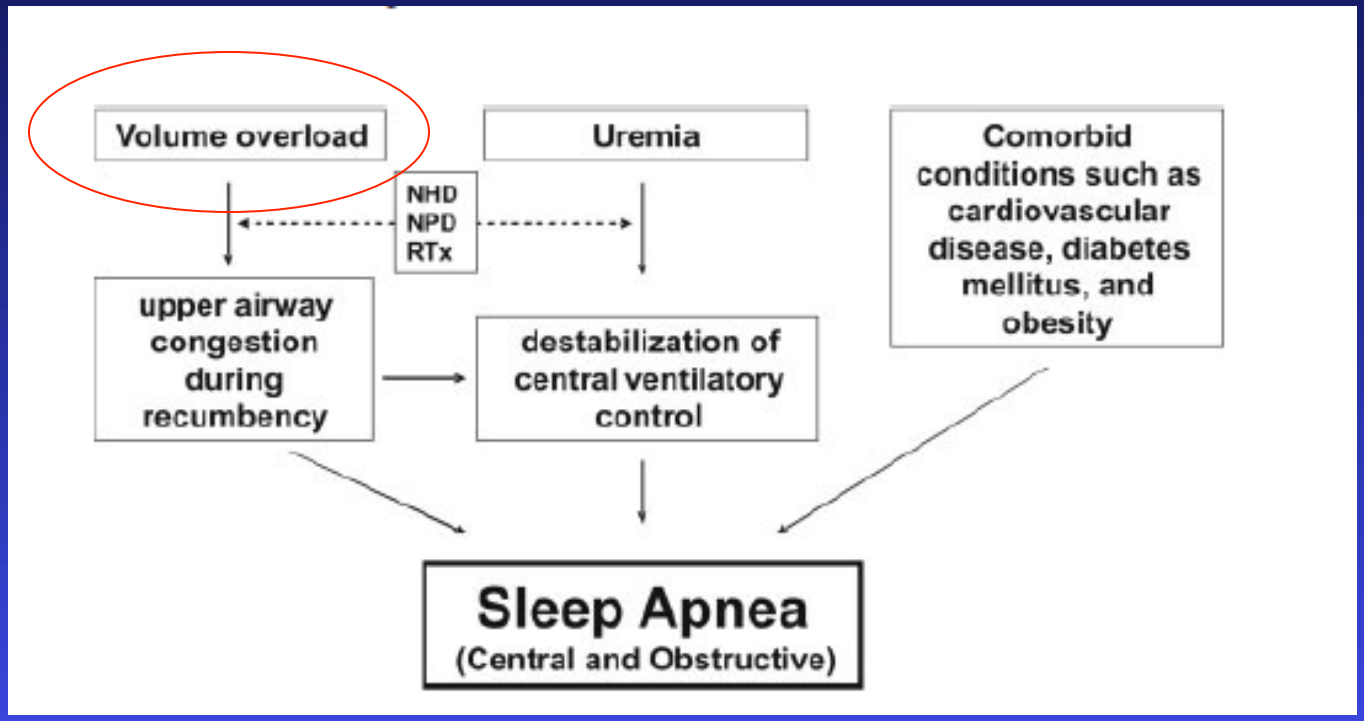
Zoccali et al – JASN 2002

Plasma Norepinephrine Predicts Survival and Incident Cardiovascular Events in Patients With End-Stage Renal Disease



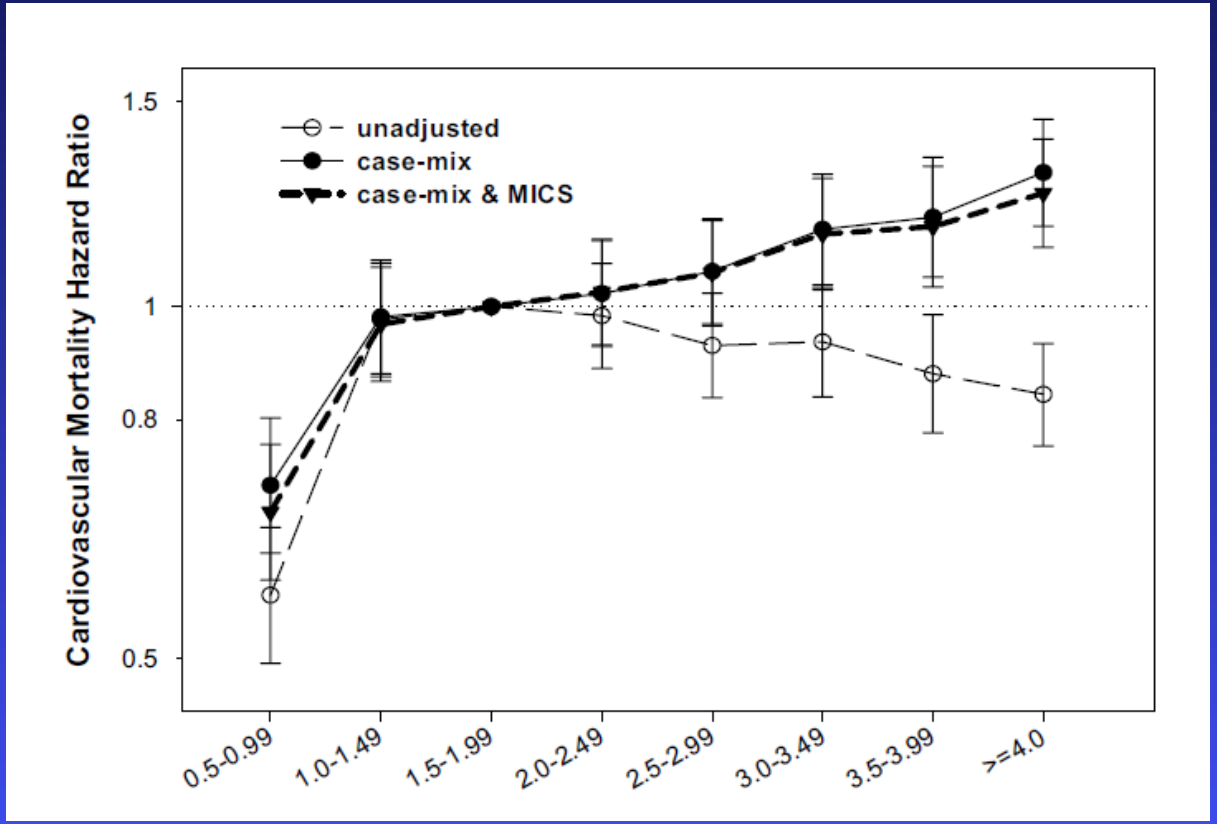
(*Circulation*. 2002;105:1354-1359.)

Pathophysiologic Explanations of SA in ESRD



Fluid Retention Is Associated With Cardiovascular Mortality in Patients Undergoing Long-Term Hemodialysis

Kamyar Kalantar-Zadeh, MD, MPH, PhD; Deborah L. Regidor, MPH, PhD;
Csaba P. Kovesdy, MD; David Van Wyck, MD; Suphamai Bunnapradist, MD;
Tamara B. Horwich, MD; Gregg C. Fonarow, MD

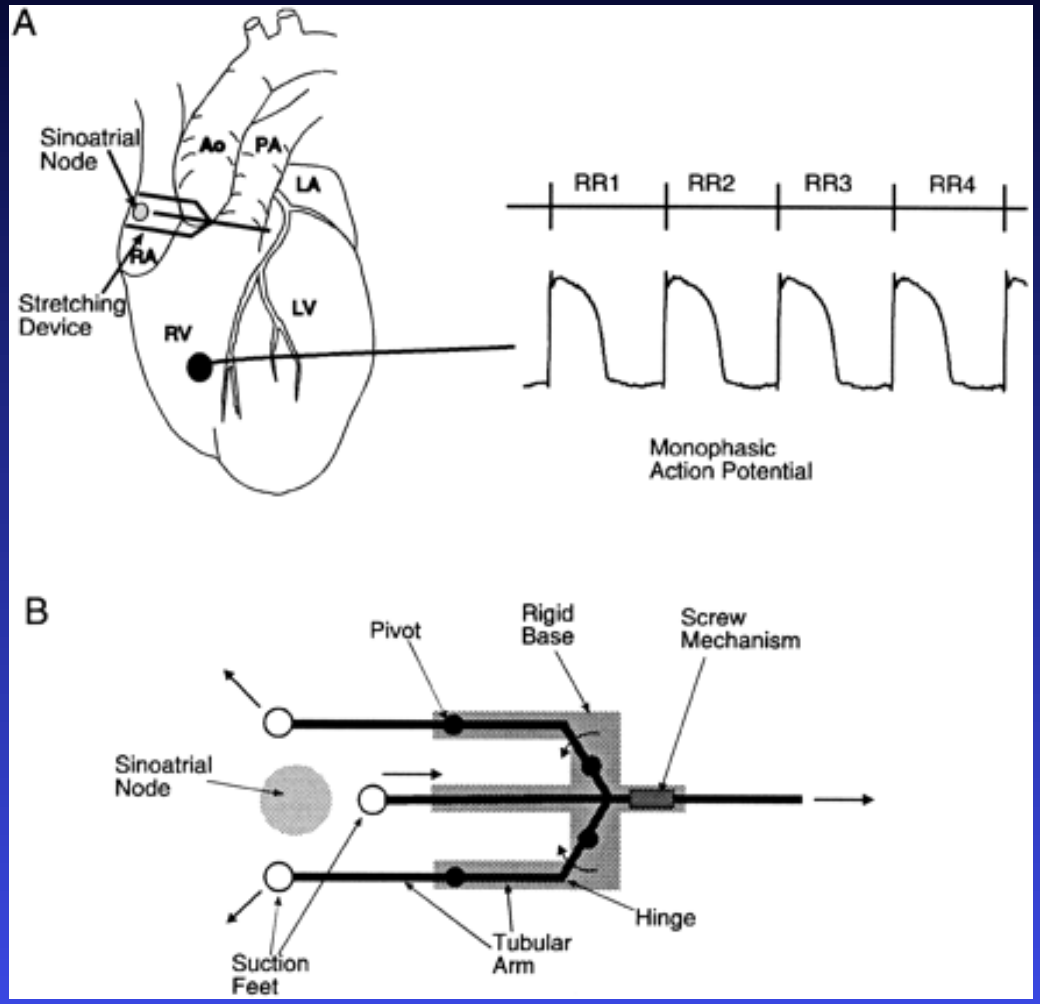


Kalantar-Zadeh et al – Circ 2009

Are there other stimuli for SNS over-activity in uremia?

- YES! → Salt / Volume overload
- Cardiac
  - Changes in cardiac dimensions will lead to impairments in SNS/vagal balance
  - Rapid ultrafiltration → SNS overactivity
- Sleep Apnea

Mechanical Stretch: HRV alterations



Horner et al – Circ 1996

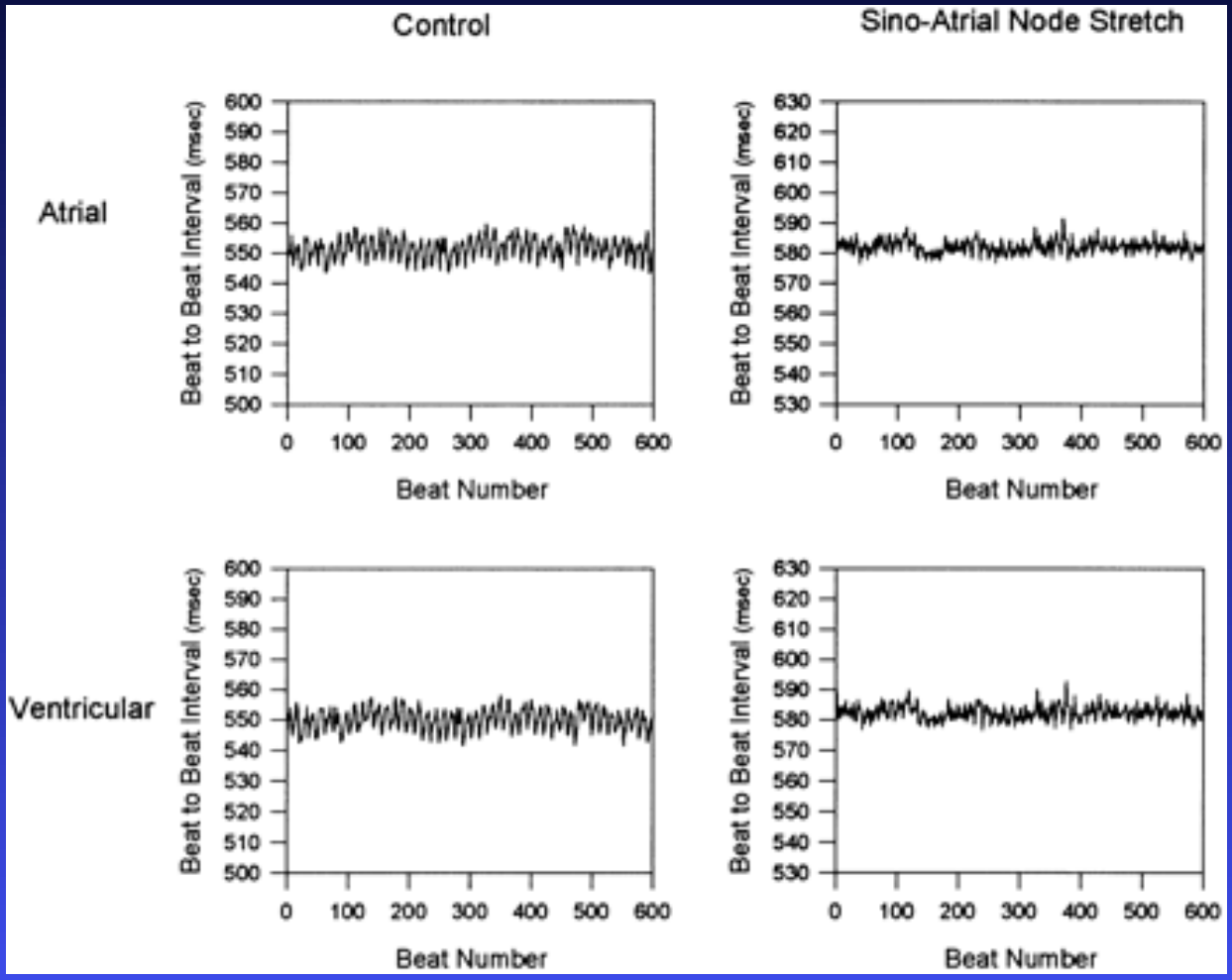
Power spectral analysis of heart rate variability

- Non-invasive measurement
- Capable of assessing dynamic changes in the autonomic control of heart rate
- Identification of superimposed oscillations which contribute to variations in heart rate

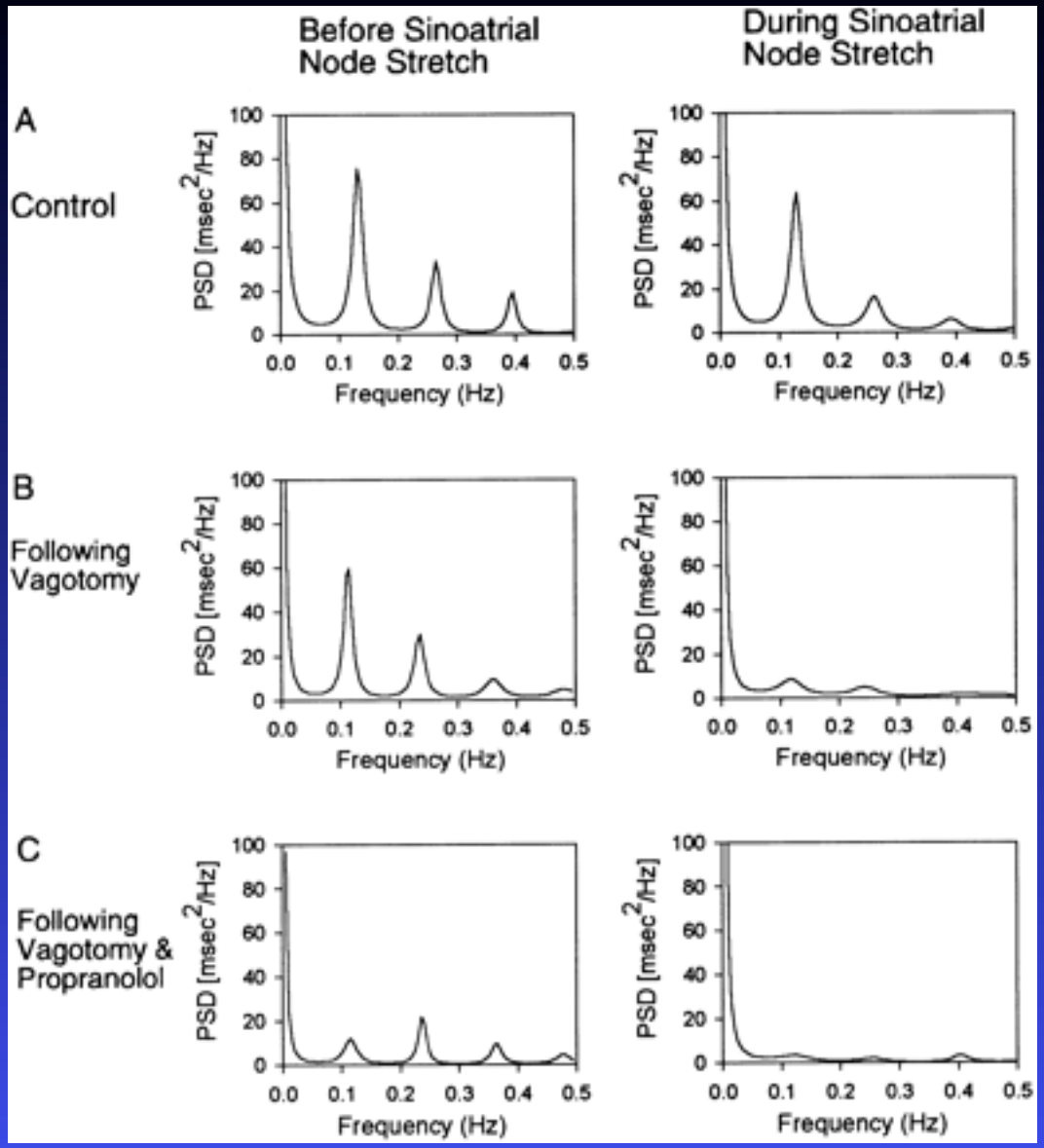
Heart rate variability in normal animals and humans

- Interpretation of PSA of HRV:
  - LF (0.05 – 0.15 Hz) : SNS
  - HF (> 0.15 Hz) : PNS
    - Administration of atropine or other agents

    virtually abolished the HF component of HRV
    - In dogs, an increase in LF power was observed during baroreceptor unloading with NTG and was prevented by prior bilateral stellectomy



Horner et al – Circ 1996



Horner et al – Circ 1996

Implications

- Recurrent Stretch / Increase in left atrium:
  - **Volume / Salt overload**
  - **May lead to sustained SNS overactivity**

Alterations in upper airway cross-sectional area in response to lower body positive pressure in healthy subjects

Table 2 Influence of lower body positive pressure (LBPP) on physiological variables

	Baseline	1 min	5 min	p Value for time × treatment interaction
Leg fluid volume (l)				
Control	4.67 (0.18)	4.67 (0.18)	4.66 (0.18)	
LBPP	4.57 (0.19)*	4.41 (0.19)*†	4.43 (0.19)*†	<0.001
Change in neck circumference (%)				
Control	–	−0.01 (0.02)	0.00 (0.05)	
LBPP	–	0.33 (0.05)*†	0.28 (0.06)*†	<0.001

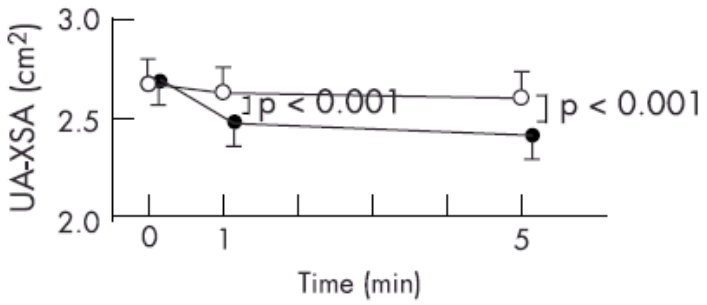


Figure 2 Grouped data showing changes in upper airway cross-sectional area (UA-XSA) in response to lower body positive pressure (LBPP); $p<0.001$ for time×treatment interaction (two-way repeated measures ANOVA). Compared with the control period, UA-XSA decreased significantly at both 1 and 5 min after applying LBPP. p Values shown in plots are adjusted for multiple comparisons by Tukey test.

Relationship between Overnight Rostral Fluid Shift and Obstructive Sleep Apnea in Nonobese Men

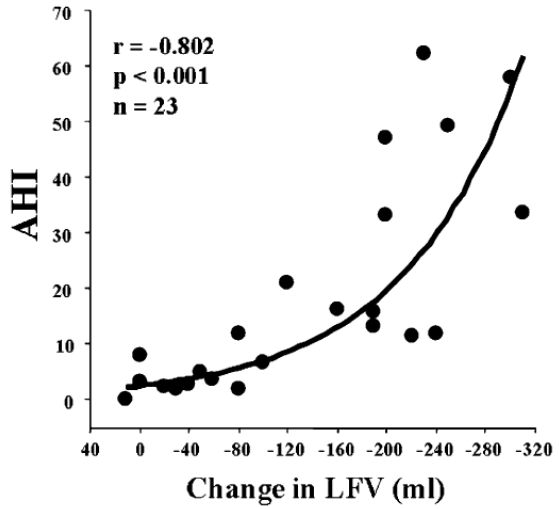


Figure 1. Relationship between the overnight change in leg fluid volume (LFV) and the apnea–hypopnea index (AHI).

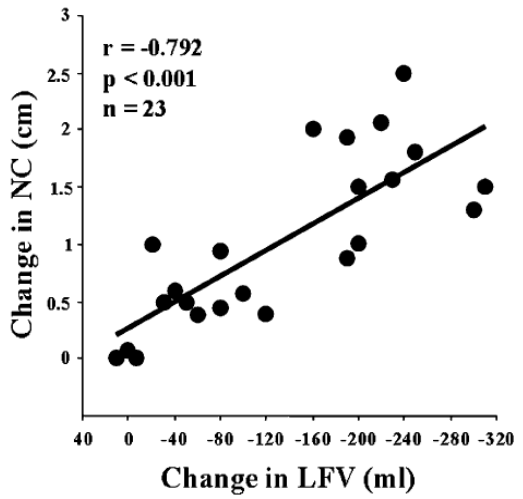
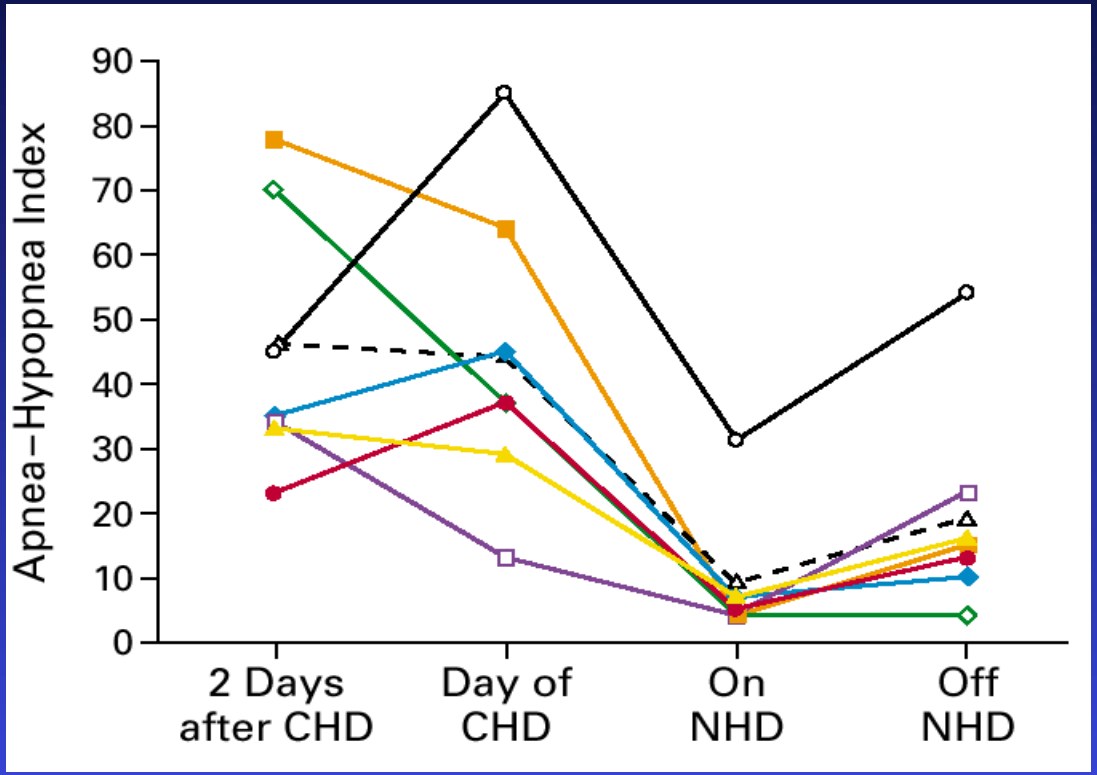


Figure 2. Relationship between the overnight change in LFV and the change in neck circumference (NC).

Bradley et al – Am J Resp Crit Care Med 2009

Correction of Sleep Apnea with NHD

The first 14 patients of the Nocturnal Hemodialysis project in Toronto. 8 patients had sleep apnea (AHI>15/hr)



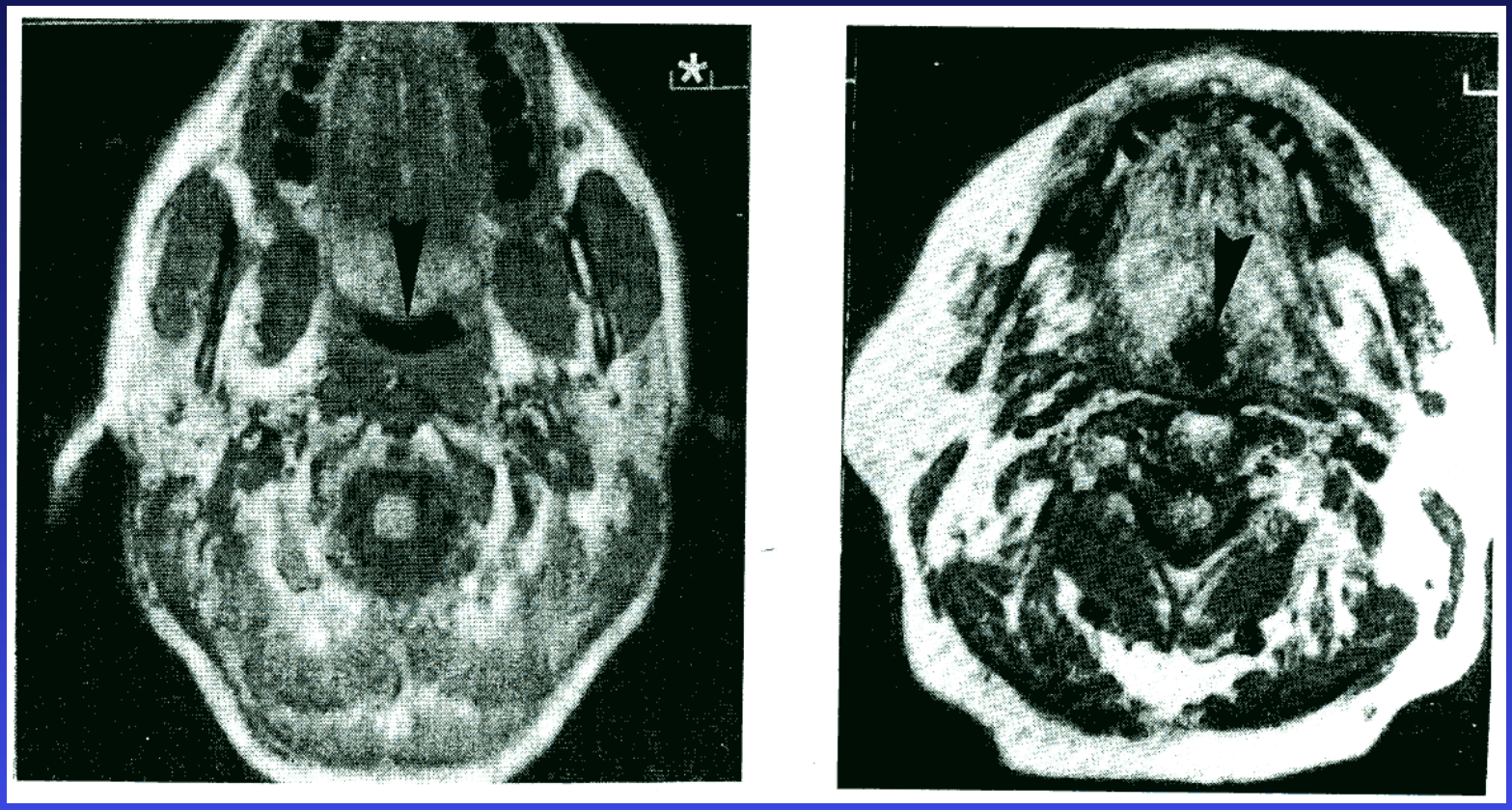
AHI decreased from 46±19 to 9±9 p=0.006
Minimum O_2 sat increased from 89.2±1.8 to 94.1±1.6 p=0.005

Hanly P, Pierratos A. NEJM 2001

Why would NHD correct sleep apnea?

ECF volume vs. Uremia or Both?

ECF volume overload: upper airway edema?



Normal Subject

Sleep Apnea

Nocturnal haemodialysis increases pharyngeal size in patients with sleep apnoea and end-stage renal disease

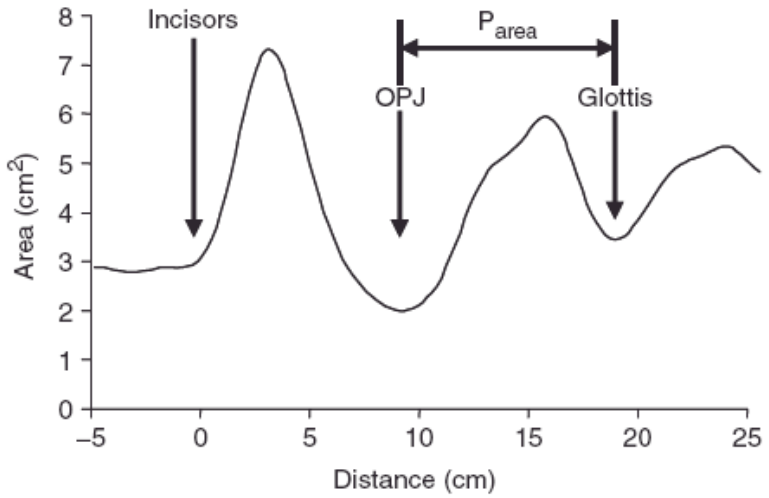


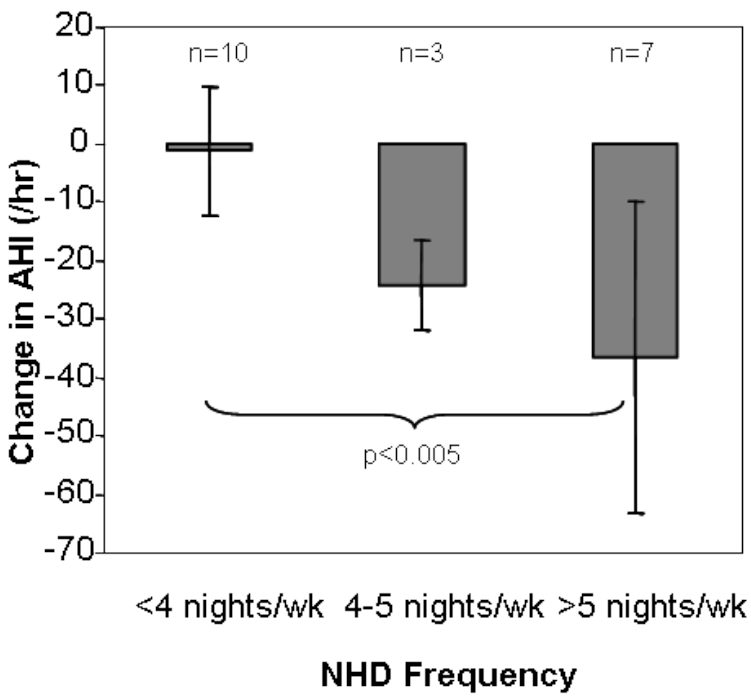
Fig. 1. Example of a typical pharyngogram. The vertical axis is cross-sectional area and the horizontal axis is the distance into the airway, with 0.0 cm corresponding to the position of the incisor teeth. Mean pharyngeal cross-sectional area is calculated between the oro-pharyngeal junction (OPJ) and the glottis.

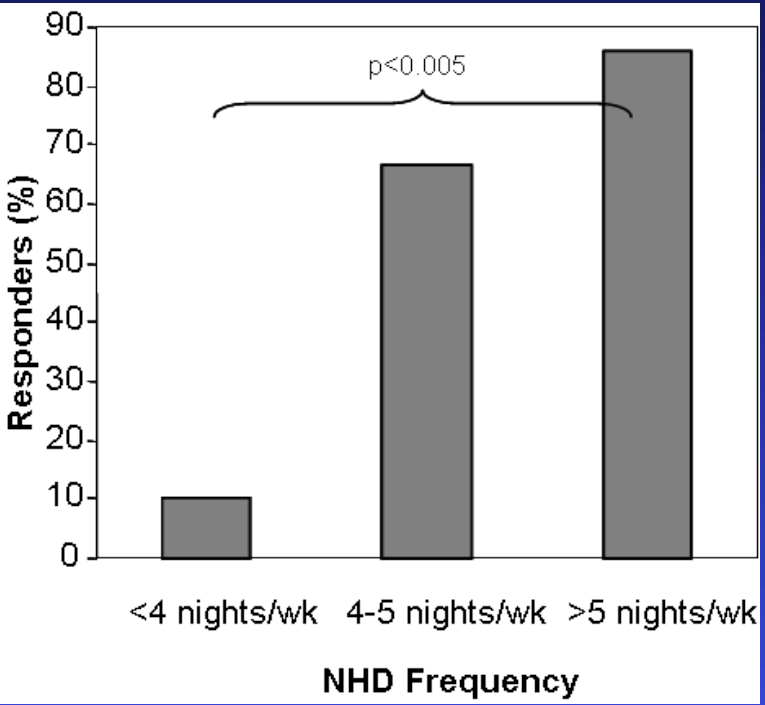
NHD → Increases
In pharyngeal size

3.17 ± 0.68 to 3.86 ± 0.67 cm^2

Beecroft et al – NDT 2008

The Impact of Nocturnal Hemodialysis on Sleep Apnea is Dose-dependent





Beecroft J et al ATS 2006

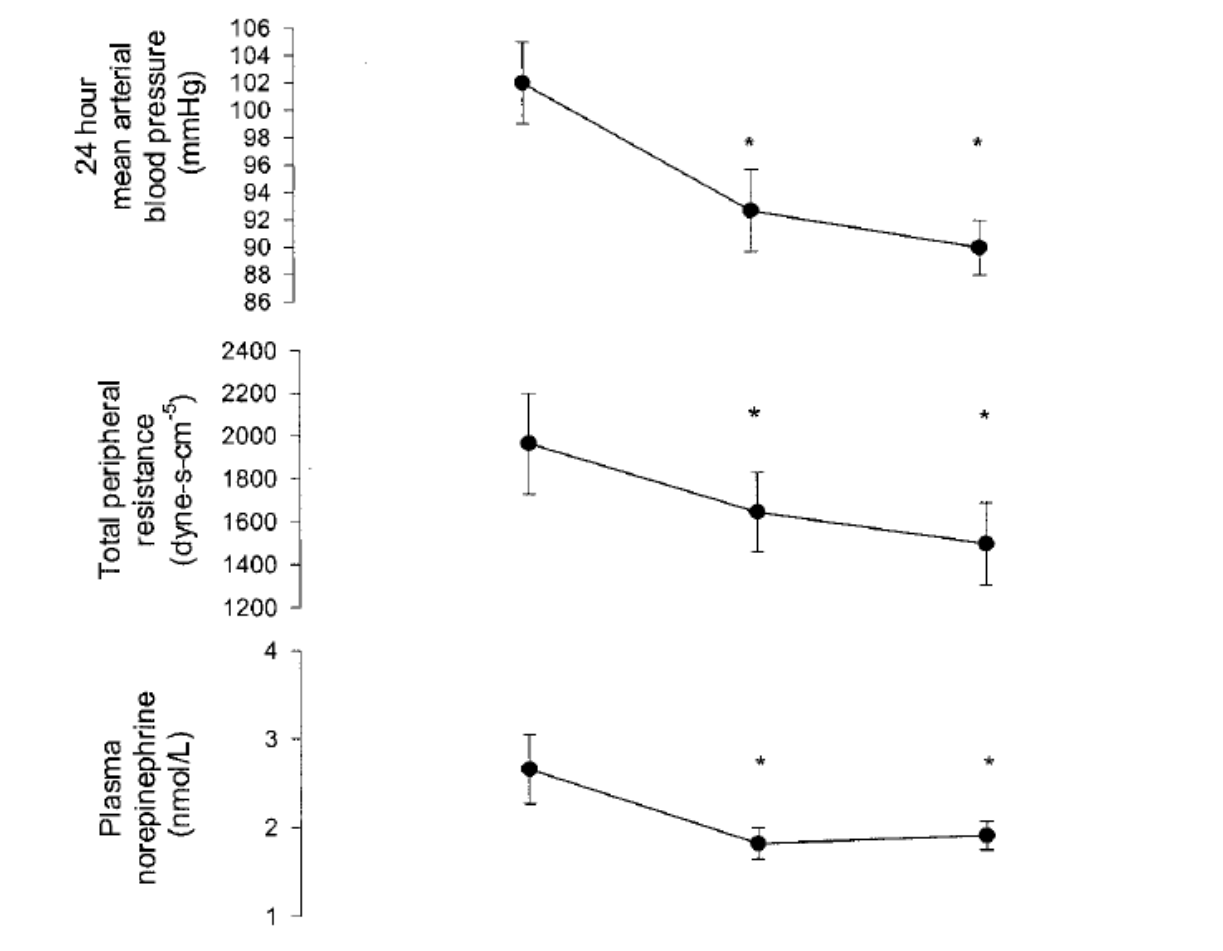
Effects of NHD on HRV during sleep

	Patients (n=9)			Normal Subjects (n=10)
Variables	CHD1	CHD2	NHD	Control
TST (hours)	5.4 ± 0.2	5.5 ± 0.2	5.3 ± 0.2	5.8 ± 0.2
AHI (per hour)	29.2 ± 9.9[3]	30.2 ± 9.8[3]	7.2 ± 3.3[1,2]	4.6 ± 1.8
%TST SaO_2 < 90%	15.4 ± 7.2[3]	12.5 ± 7.5[3]	3.5 ± 3.4[1,2]	0.2 ± 0.2
RR intervals (ms)	829 ± 35[3]	795 ± 29[3]	912 ± 48[1,2]	978 ± 35
LF	202 ± 94	85 ± 36	356 ± 151	4788 ± 2648
HF	100 ± 44[3]	48 ± 15[3]	712 ± 256[1,2]	6726 ± 4555
LF/LF+HF	0.60 ± 0.08	0.59 ± 0.10	0.39 ± 0.06	0.42 ± 0.04
HF/LF+HF	0.14 ± 0.02[3]	0.17 ± 0.05[3]	0.32 ± 0.07[1,2]	0.42 ± 0.05
LF/HF	2.17 ± 0.54[3]	3.57 ± 1.81[3]	0.75 ± 0.22[1]	0.71 ± 0.11

[1] $p<0.05$ compared with CHD1, [2] $p<0.05$ compared with CHD2, [3] $p<0.05$ compared with normal

Chan et al – KI 2005

Short term vascular effects of NHD



Chan et al Hypertension 2003

Improvement in Sleep Apnea during Nocturnal Peritoneal Dialysis Is Associated with Reduced Airway Congestion and Better Uremic Clearance

Table 2. Polysomnographic data while on NPD or CAPD (n = 38)

	On NPD	On CAPD	P
Total sleep time (h)	5.0 ± 1.60	5.55 ± 1.41	NS
Sleep efficiency[a]	57.4 ± 14.4	62.8 ± 12.7	NS
Stage of sleep (% of total sleep time)			
rapid eye movement	18.2 ± 10.5	16.7 ± 8.6	NS
stage 1, 2	78.8 ± 22.1	79.3 ± 20.0	NS
slow wave (stage 3, 4)	1.9 ± 3.2	4.0 ± 3.6	NS
AHI (no./h)	9.6 ± 2.74	21.5 ± 4.15	<0.001
subjects with AHI > 15 (n, %)	8 (21.1%)	16 (42.1%)	0.008
subjects with AHI > 10 (n, %)	10 (26.3%)	19 (50%)	0.004
subjects with AHI > 5 (n, %)	11 (28.9%)	22 (57.9%)	0.001
Duration with oxygen saturation < 90% (min)	64.3 ± 15.8	94.8 ± 20.5	0.025
Arousals (no./h)	16.6 ± 9.8	26.6 ± 16.4	<0.001
Periodic leg movement (no./h)	0.5 ± 0.21	1.4 ± 0.35	0.007

[a]Ratio of total sleep time to total time in bed. Data are presented as mean (± SD). AHI, apnea-hypopnea index (*i.e.*, average number of episodes of apnea and hypopnea per hour of sleep).

Tang et al CJASN 2009

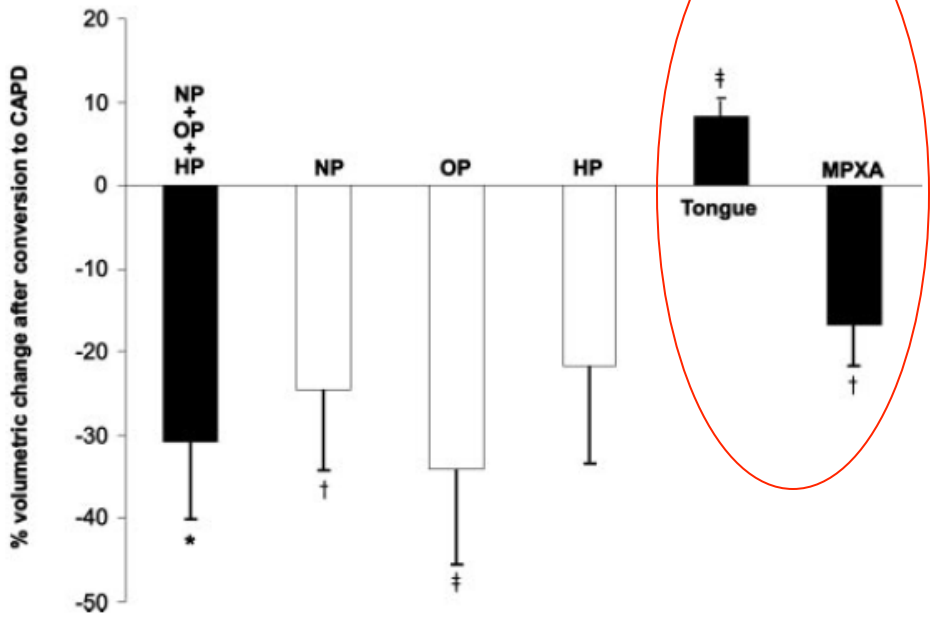
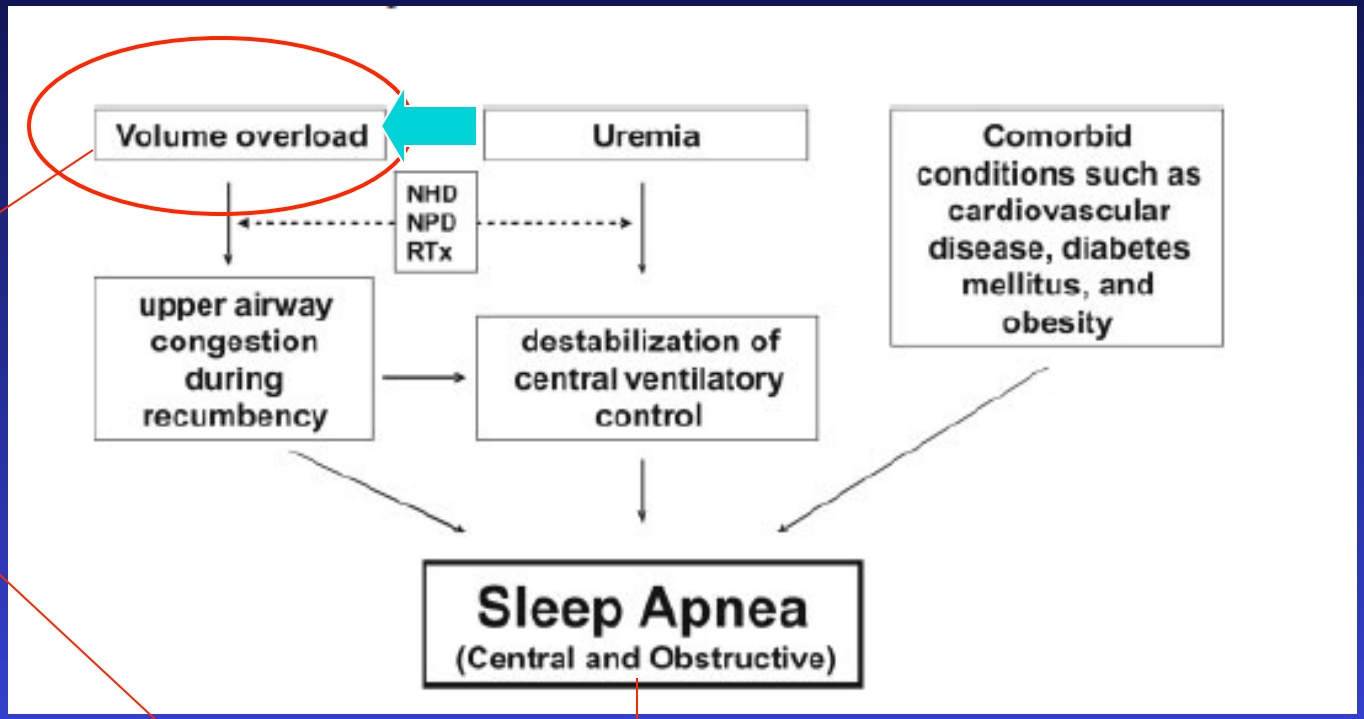


Figure 5. Percentage volumetric change in the various anatomic sites of the upper airway after conversion to CAPD ($n = 14$). $^{*}P = 0.004$, $^{\dagger}P = 0.04$, $^{\ddagger}P = 0.02$ *versus* values obtained during NPD. NP, nasopharynx; OP, oropharynx; HP, hypopharynx; MPXA, minimal pharyngeal cross-sectional area. Error bars are mean ± SEM.

Summary



Incr. SNS

Incr. CVS events
Incr. mortality

Acknowledgment

- Home hemodialysis units
  - TGH , HRRH
- Human Cardiovascular Physiology Group
  - JS Floras
- Stem Cell Group
  - S Verma
  - H Messner
- Genomics
  - Peter Liu
- E-Health Group
  - A Jadad, P Rossos, J Granton, R Owens, A Easty, P Milgrim
- Div of Nephrology / UHN
- CIHR, HSFO, BUL – Medicine, PSI
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