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

\textsuperscript{a}Data are means ± SD. NREM, non–rapid eye movement; REM, rapid eye movement.
\textsuperscript{b}NS = P > 0.05.
\textsuperscript{c}Log-log transformation used for test of group differences.
\textsuperscript{d}Log transformation used for test of group differences.
\textsuperscript{e}The percentage of total sleep time with an oxygen saturation of <90%.
“Classical Model” - Sleep Apnea

- Repetitive cycles of apnea, hypoxia, hypercapnia and arousal
  - Abrupt generation of negative intra-thoracic pressure
  - Sudden and profound changes in cardiac loading conditions
  - Trigger of central sympathetic outflow to heart and periphery

- Gas exchange abnormalities
  - Nocturnal Hypoxemia

- Sleep Fragmentation
  - Impaired quality of life

- Nocturnal Hypoxemia
  - Coronary artery calcification
  - Oxidative stress

- Sympathetic Hyperactivity
  - Left Ventricular Hypertrophy / Hypertension
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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units of Increase</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1 yr</td>
<td>1.07 (1.02 to 1.13)</td>
<td>0.007</td>
</tr>
<tr>
<td>Average nocturnal</td>
<td>1%</td>
<td>0.77 (0.62 to 0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>SaO2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1 mmol/L</td>
<td>0.49 (0.25 to 0.97)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Fatal and non fatal cardiovascular events

Cumulative Survival

Time (months)
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

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
Implications

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

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 min</th>
<th>5 min</th>
<th>p Value for time × treatment interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg fluid volume (L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.67 (0.18)</td>
<td>4.67 (0.18)</td>
<td>4.66 (0.18)</td>
<td></td>
</tr>
<tr>
<td>LBPP</td>
<td>4.57 (0.19)*</td>
<td>4.41 (0.19)*†</td>
<td>4.43 (0.19)*†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in neck circumference (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>–</td>
<td>–</td>
<td>0.00 (0.05)</td>
<td></td>
</tr>
<tr>
<td>LBPP</td>
<td>–</td>
<td>0.33 (0.05)*†</td>
<td>0.28 (0.06)*†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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).

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 O₂ 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

NHD $\rightarrow$ Increases In pharyngeal size

$3.17 \pm 0.68$ to $3.86 \pm 0.67 \text{ cm}^2$

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.

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

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

<sup>1</sup> p<0.05 compared with CHD1,  <sup>2</sup> p<0.05 compared with CHD2,  <sup>3</sup>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>
<thead>
<tr>
<th>Table 2. Polysomnographic data while on NPD or CAPD (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On NPD</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Total sleep time (h)</td>
</tr>
<tr>
<td>Sleep efficiency&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage of sleep (% of total sleep time)</td>
</tr>
<tr>
<td>rapid eye movement</td>
</tr>
<tr>
<td>stage 1, 2</td>
</tr>
<tr>
<td>slow wave (stage 3, 4)</td>
</tr>
<tr>
<td>AHI (no./h)</td>
</tr>
<tr>
<td>subjects with AHI &gt; 15 (n, %)</td>
</tr>
<tr>
<td>subjects with AHI &gt; 10 (n, %)</td>
</tr>
<tr>
<td>subjects with AHI &gt; 5 (n, %)</td>
</tr>
<tr>
<td>Duration with oxygen saturation &lt; 90% (min)</td>
</tr>
<tr>
<td>Arousals (no./h)</td>
</tr>
<tr>
<td>Periodic leg movement (no./h)</td>
</tr>
</tbody>
</table>

<sup>a</sup>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).
Figure 5. Percentage volumetric change in the various anatomic sites of the upper airway after conversion to CAPD ($n = 14$). *$P = 0.004$, †$P = 0.04$, ‡$P = 0.02$ 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

- NIDDK
Your tests reveal that you are retaining fluids!