II Sleep-disordered breathing

Sleep disordered breathing (SDB)

Scope of SDB

- Obstructive sleep apnoea (OSA)
- Central sleep apnoea (CSA)
- Hypoventilation (daytime hypercapnia)
- SDB in children
II Sleep-disordered breathing

OSA – current concept and definition

- Functional disorder characterized by repetitive obstructions of the upper airway (UA) during sleep
- Causing sleep disruption that the patient may or may not perceive
- Often causing or aggravating functional complaints and affecting comorbid conditions, e.g. arterial hypertension, disturbed glucose metabolism, etc.
- Treatment aims at stabilizing the UA during sleep

OSA - Update

Update: What’s new?

- Huge annual scientific output
  # hits on OSA in PubMed 2012-2014 > 7500
  yet limited data and often conflicting results
- Capita selecta on OSA:
  – Pathophysiology
  – Comorbidities
  – Treatment
  – Implications for clinical practice
II Sleep-disordered breathing

Pathophysiology

• Passive narrowing of the UA during sleep is the cause of increased resistance to inspiratory flow

• The pattern of inspiratory effort during obstruction is typically incremental, to overcome the increased resistance

• The crescendo effort is usually futile and an arousal is required to undo the obstruction

• Classical model: the ‘balance of forces’ theory
II Sleep-disordered breathing

Pathophysiology – classical paradigm

**BALANCE OF FORCES**

1. **CONSTRICITING FORCES**
   - Tissue pressure ($P_{tiss}$)
   - Atmospheric pressure ($P_{atm}$)
   - Intraluminal pressure ($P_{lumen}$)
   - Gravity ($P_{g}$)
   - Surface tension ($P_{surf}$)

2. **DILATING FORCES**
   - Action of UA dilator muscles ($P_{mus}$)
   - Tracheal tug ($P_{tug}$)

---

Pathophysiology – classical paradigm

[Diagram showing the balance of forces]

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Isono et al. JAP'97, 82, 1319
II Sleep-disordered breathing

Pathophysiology – classical paradigm

Isono et al. JAP’97, 82, 1319

Pcrit is a measure of the anatomic characteristics of the UA

Pathophysiology – new paradigm

Defining Phenotypic Causes of Obstructive Sleep Apnea
Identification of Novel Therapeutic Targets

Danny J. Eckert1,2, David P. White1, Amy S. Jordan1,2, Atul Mahotra1, and Andrew Wellman1

1Division of Sleep Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts; 2Neuroscience Research Australia and the School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia; and 3Melbourne School of Psychological Sciences, University of Melbourne, Parkville, Victoria, Australia

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Internet address: www.atsjournals.org
II Sleep-disordered breathing

Pathophysiology – new paradigm

- Apneic [58] and non-apneic [17] subjects (M+F)
- Determination of AHI and:
  - $P_{\text{crit}}$ (anatomic factor)
  - Arousal threshold
  - Loop gain (respiratory control instability)
  - Genioglossus muscle responsiveness
- Pathophysiologic traits were quantified (‘PALM’ score) and varied substantially among subjects

Eckert et al. AJRCCM’13, 188, 996
II Sleep-disordered breathing

Pathophysiology – new paradigm

Loop gain = 4.2 / -1.4 = -3

Eckert et al. AJRCCM’13, 188, 996
Pathophysiology – The PALM scale

<table>
<thead>
<tr>
<th>PALM #</th>
<th>Pcrit</th>
<th>% Pts</th>
<th>Features</th>
<th>Treatment targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;+2</td>
<td>23%</td>
<td>Highly collapsible UA severe OSA</td>
<td>Anatomic intervention (CPAP)</td>
</tr>
<tr>
<td>2a</td>
<td>-2 to +2</td>
<td>21%</td>
<td>Moderately collapsible UA only anatomically driven overall severe OSA (wide range)</td>
<td>Anatomic intervention (CPAP, MRA, …)</td>
</tr>
<tr>
<td>2b</td>
<td>-2 to +2</td>
<td>37%</td>
<td>Moderately collapsible UA one or more non-anatomic factors are important overall severe OSA (wide range)</td>
<td>Anatomic plus nonanatomic interventions (e.g. oxygen supplement, sedatives)</td>
</tr>
<tr>
<td>3</td>
<td>&lt;-2 hPa</td>
<td>19%</td>
<td>Slightly collapsible UA all have one or more non-anatomic factors mild to moderate OSA (wide range)</td>
<td>Combination of targeted therapies, plausibly with nonanatomic interventions</td>
</tr>
</tbody>
</table>

Eckert et al. AJRCCM’13, 188, 996

Pathophysiology – “Phenotyping”

Emergence of Obstructive Sleep Apnea Phenotyping
From Weak to Strong!
Editorial by S. Parathasarathy

Physiologic phenotyping of OSA may lead to ‘personalized treatment’

OSA in Older Adults is a Distinctly Different Physiological Phenotype

Obstructive Sleep Apnea in Older Adults is a Distinctly Different Physiological Phenotype

Bradley A. Edwards, PhD; Andrew Wwwatts, MD, PhD; Scott A. Sands, PhD; Robert L. Owens, MD; Danny J. Eckert, PhD; David P. White, MD; Atul Malhotra, MD

Division of Sleep Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; Precise Research Associates (PRA) and the University of New South Wales, Randwick, Sydney, New South Wales, Australia; Division of Pulmonary and Critical Care Medicine, University of California San Diego, San Diego, CA

SLEEP 2014;37(7):1227-1236.
II Sleep-disordered breathing

Comorbidities of OSA

Moderate to severe OSA is associated with:

- Arterial hypertension (AHT) ***new studies***
- Cardiovascular morbidity and mortality
- Impaired glucose metabolism, dyslipidemia
- Systemic inflammation and oxidative stress
- New evidence on cancer
Comorbidities of OSA – AHT

**Timeline:**

- **90’s:** trials with deficient study design
  
  Stradling et al. Sleep ’97: “Sleep apnea and hypertension - what a mess!”

- **00’s:** adequate RCT’s: significant decrease in 24-h BP
  
  Pepperell et al. Lancet 2002
  Becker et al. Circulation 2003

- **10’s:** Cohort studies and meta-analyses
  
  O’Connor et al. SHHS. AJRCCM 2009
  Cano-Pumarega et al. Vitoria Sleep cohort. AJRCCM 2011
II Sleep-disordered breathing

OSA – AHT: carefully conducted studies

- Pepperell et al. Lancet 2002
- Becker et al. Circulation 2003

OSA – AHT: current state of knowledge

- About half of OSA patients have AHT
- About a third of AHT patients have OSA
- About 80% of pts with resistant AHT have OSA; OSA may be the leading cause in about 2/3
- CPAP decreases MAP by about 2 mmHg
- Some parameters may predict the antihypertensive effect of CPAP therapy
- New evidence on incident and resistant AHT
II Sleep-disordered breathing

OSA: new onset AHT in prospective cohorts

- **Barbé**: 725 OSA (AHI > 20; ESS < 10), 50% AHT, randomized to CPAP vs no treatment for 4 years
- Outcome: incidence of new AHT or CV events: (n/100 person-years) CPAP = 11.0  untreated = 9.2 (NS)
- No difference in both groups when stratified for AHI (OSA severity)
- Post hoc analysis: better results in CPAP adherent patients
OSA: new onset AHT in prospective cohorts

- **Marin**: follow-up of 1889 non-hypertensive subjects (OSA + CPAP, OSA - CPAP, non-OSA) for > 10 years
- **Outcome**: incidence of new AHT: 705 cases

<table>
<thead>
<tr>
<th></th>
<th>Non-OSA</th>
<th>Ineligible</th>
<th>Declined</th>
<th>Poor adherence</th>
<th>Adherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/100 p-y</td>
<td>2.2</td>
<td>3.3</td>
<td>5.8</td>
<td>5.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>1.0</td>
<td>1.3</td>
<td>2.0</td>
<td>1.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

- Compared with non-OSA, OSA was associated with increased adjusted risk of incident AHT
- CPAP therapy was associated with a lower risk of AHT

**Comment**: “However, the potential bias related to group assignment based on adherence to therapy, which is inherent in observational study design, precludes definitive causal conclusions regarding the affect of CPAP therapy on the risk for hypertension in OSA.”
II Sleep-disordered breathing

OSA: Impact of CPAP on resistant AHT

Original Investigation
Effect of CPAP on Blood Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension
The HIPARCO Randomized Clinical Trial
Martinez-Garcia et al. JAMA 2013—Vol 310, 2407-15

Blood Pressure Improvement with Continuous Positive Airway Pressure is Independent of Obstructive Sleep Apnea Severity
José-Durán-Carrillo, M.D., Ph.D.1, Felipe-Lozoya, M.D., Ph.D.1, Fernando-Barba, M.D., Ph.D.1, Yassiel-Sánchez-de-la-Torre, Ph.D.1, Aníbal-Rahola, M.D., Ph.A.A.S.M.1
Journal of Clinical Sleep Medicine, Vol. 10, No. 4, 2014

OSA: Effect of CPAP on resistant AHT (RAHT)

- **Martinez-Garcia**: 194 OSA (AHI ± 40) and RAHT were randomly assigned to CPAP (n = 98) or no CPAP (n = 96) for 3 months

- Outcome: decrease of BP parameters; BP dipping (ITT) MBP (3.1mm Hg) and DBP but not SBP were significantly lower in CPAP treatment arm, which had also more dippers (35.9 vs 21.6%)

- Hours of CPAP use correlated with decrease of BP

- So, favourable effects of CPAP were demonstrated
OSA: Effect of CPAP on resistant AHT (RAHT)

- **Bakker**: meta-analysis of 8 RCTs including 968 OSA pts without major comorbidities; CPAP vs non-therapeutic control conditions
- SBP was reduced by 2.3 mm Hg and DBP by 1.8 mm Hg in CPAP vs control. Various parameters affected the outcome of CPAP treatment.
- Conclusions: OSA pts with uncontrolled hypertension are likely to gain the largest benefit from PAP in terms of a substantial reduction in BP, even after controlling for disease severity.

OSA, AHT and CPAP: summary

- Additional evidence for (1) risk of new-onset AHT in OSA; (2) beneficial effect of CPAP-therapy on BP
- Predictors of improvement of BP with CPAP-therapy:
  1. good adherence
  2. young age
  3. baseline BP (biggest effects in pts with higher-end BP)
  4. daytime sleepiness (larger falls in sleepier patients)
  5. severity of OSA
- Yet effect of CPAP << effect of AHT drugs
II Sleep-disordered breathing

OSA and cancer

Intermittent hypoxia enhances cancer progression in a mouse model of sleep apnoea
Almendros et al. ERJ 2012, 39, 215

Sleep-disordered Breathing and Cancer Mortality
Results from the Wisconsin Sleep Cohort Study
F. Javier Nieto¹, Paul E. Peppard¹, Terry Young¹, Laurel Finn¹, Khin Ma Hla²,³,
and Ramon Fare²

Association between Obstructive Sleep Apnea and Cancer Incidence in a Large Multicenter Spanish Cohort
Francisco Campos-Rodriguez¹, Miguel A. Martínez-García², Montserrat Martínez²,³,
Joaquín Durán-Cantolla¹, Monica de la Peña¹,³, María J. Masdeu¹,³, Monica González⁴,
Felix del Campo⁵, Inmaculada Gallego⁶, Jose M. Marín¹,³, Ferran Barbe²,³, Jose M. Montserrat¹,³,³,
and Ramon Farre¹,³ on behalf of the Spanish Sleep Network

• Almendros: conventional murine melanoma model; 6 h/day CIH (60 events/h⁻¹; 20 s of 5% O₂ - 40 s of room air)
• Growth of tumour assessed @ D8, 11, 14
• Animals sacrificed @ D14
• T-growth in CIH-mice >> control mice
• Hypothesis: CIH may stimulate angiogenesis and thus T-growth

16
II Sleep-disordered breathing

**OSA and cancer**

- **Nieto**: 22 yr follow-up > 1500 people of Wisconsin cohort
  50/112 deaths from cancer; total and cancer mortality ~ SDB

- Predictors: AHI and HO-I measured @ baseline*

- Significant association mortality – indices of SDB severity (after adjustment)

- HO-I better predictor than AHI

- This population-based epidemiologic study suggests a dose–response relation between SDB and cancer mortality

  *Pts on CPAP were included; after exclusion association became stronger

**OSA and cancer**

- **Campos-Rodriguez**: retrospective study (N=4910; 4.5 yrs)
  261 pts (5.3%) had diagnosis of cancer

- Predictors: AHI and HO-I measured @ baseline* - only HO-I seems to have predictive power

  *Pts on CPAP were included; after exclusion association was not changed
OSA and cancer

Conclusions:

- These three studies provide preliminary evidence for the role of CIH in cancer incidence / progression
- Limitations: severe hypoxia model in mice; retrospective analysis (Spain); prospective study not designed to analyze cancer outcomes (US); small number of events
- AHI instead of ODI or HO-I used as primary predictor
- These hypothesis generating studies need confirmation by large scale and long term prospective trials using correct predictor (ODI) and outcome (type of cancer) measures

Treatment of OSA
Treatment of OSA – overview

- Continuous positive airway pressure (CPAP)
- Mandibular advancement devices (MAD)
- Upper airway surgery
- Maxillo-mandibular surgery
- Body position training
- Body weight reduction
- Hypoglossal Nerve Stimulation (HNS)

CPAP vs MAD

Health Outcomes of Continuous Positive Airway Pressure versus Oral Appliance Treatment for Obstructive Sleep Apnea
A Randomized Controlled Trial

Craig L. Phillips¹, Ronald R. Grunstein²,³, M. Ali Darendellier⁴, Anastasia S. Mihailidou⁵,⁶, Vasantha K. Srinivasan⁴, Brendan J. Yee²,⁵, Guy B. Marks⁵,⁶, and Peter A. Cistulli²,⁵

¹Department of Respiratory and Sleep Medicine and ²Department of Cardiology, Royal North Shore Hospital, St. Leonards, Australia; ³NHMRC Centre for Integrative Research and Understanding of Sleep, Woolcock Institute of Medical Research, Sydney Medical School, and ⁴Department of Orthodontics, Sydney Dental Hospital and Faculty of Dentistry, University of Sydney, Sydney, Australia; ⁵Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Sydney, Australia; ⁶Kolling Medical Research Institute, Royal North Shore Hospital and University of Sydney, Sydney, Australia; and ⁷Department of Respiratory Medicine, Liverpool Hospital, Sydney, Australia

American Journal of Respiratory and Critical Care Medicine
Vol 187 (8) 879-887, 2013
II Sleep-disordered breathing

CPAP vs MAD

**Study design:**
- CPAP (ResMed S8) vs MAD (Somnodent): effects on health outcomes in ‘real-life’ treatment conditions
  - CV function, EDS, driving simulator, QoL
- Working hypothesis:
  - suboptimal efficacy with MAD is counterbalanced by better compliance relative to CPAP
  - ergo, similar overall alleviation of OSA
  - ergo, similar effectiveness of both treatments

**Methods:**
- RCT, crossover, open label
- 1 month of optimal OSA treatment with CPAP vs optimal OSA treatment with MAD
- “Optimal” = highest compliance and best efficacy with each treatment in standard clinical practice
- Intention-to-treat protocol
- Sample size calculation was based on a BP outcome; noninferiority of MAD/CPAP for the 24MAP (margin of 1.6 mm Hg): 108 completers
II Sleep-disordered breathing

CPAP vs MAD

177 Patients assessed for eligibility
- 53 screen failures
  - 16 - Did not fulfil dental criteria
  - 8 - Dental treatment too expensive
  - 3 - AHI > 10
  - 2 - Declined with no reason
  - 2 - Declined after considering dental therapy
  - 1 - Exaggerated gag reflex
  - 1 - Protocol violation
  - 1 - AHI too severe (59.8)
  - 1 - Recruitment closed

126 Randomised

Baseline Assessment

122 Entered Acclimatisation phase

4 withdrawals
- 1 - Work demands
- 1 - Time commitments
- 1 - SAE
- 1 - Protocol violation

CPAP vs MAD

122 Entered Acclimatisation phase

62 Acclimatised to CPAP then MAD
- 7 Early withdrawals
  - 1 - Time commitments
  - 1 - Not compliant
  - 1 - Personal reasons & time
  - 1 - Unable to tolerate CPAP and wished to withdraw
  - 1 - Serious adverse event

55 completed acclimatisation

60 Acclimatised to MAD then CPAP
- 2 Early withdrawals
  - 1 - Time commitments
  - 1 - Broken tooth & time

58 completed acclimatisation
II Sleep-disordered breathing

CPAP vs MAD

55 completed acclimatisation

2 weeks washout

58 completed acclimatisation

110 Entered Treatment phase

3 Early withdrawals
1 - Unable to tolerate either device
2 - No perceived treatment benefit
3 - Adverse Event

56 completed CPAP first

54 completed MAD first

CPAP vs MAD

56 completed CPAP first

2 weeks washout

56 Completers

308 Completers

54 completed MAD first

52 completed CPAP last

52 Completers

2 Early withdrawals
1 - Personal reasons & time
2 - Not compliant with protocol
II Sleep-disordered breathing

CPAP vs MAD

TABLE 1. BASELINE CHARACTERISTICS OF ALL RANDOMIZED PATIENTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number randomized</td>
<td>126</td>
<td>—</td>
</tr>
<tr>
<td>Mild/moderate/severe OSA</td>
<td>23/8/34</td>
<td>—</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/F</td>
<td>102/24</td>
<td>—</td>
</tr>
<tr>
<td>Age, yr</td>
<td>49.5 (11.2)</td>
<td>22-78</td>
</tr>
<tr>
<td>Anthropometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.3 (5.5)</td>
<td>18.7-55.5</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>101.2 (15.8)</td>
<td>37.5-139</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>40.3 (3.8)</td>
<td>32-56</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI, h⁻¹</td>
<td>25.6 (12.3)</td>
<td>10.2-68.8</td>
</tr>
<tr>
<td>ODI, %</td>
<td>20.8 (12.5)</td>
<td>1.7-67.6</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>94.7 (3.6)</td>
<td>90.5-98.5</td>
</tr>
<tr>
<td>Minimum SpO₂</td>
<td>82.7 (7.6)</td>
<td>62-93</td>
</tr>
<tr>
<td>Arousal index, h⁻¹</td>
<td>34.3 (15.8)</td>
<td>8.1-79.6</td>
</tr>
<tr>
<td>Epworth Sleepiness Score</td>
<td>9.1 (4.2)</td>
<td>1-18</td>
</tr>
<tr>
<td>Office blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>123.7 (14.1)</td>
<td>98-163</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80.6 (9.1)</td>
<td>67-106</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>48</td>
<td>—</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>Reflux</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td>Antithrombotic</td>
<td>11</td>
<td>—</td>
</tr>
</tbody>
</table>

• 82% AHI >=15/h
• 81% M
• Overweight to obese
• 50% ESS > 10
• 38% on AHD

CPAP vs MAD

TABLE 2. INTENTION-TO-TREAT POLYSOMNOGRAPHY AND SELF-REPORTED COMPLIANCE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) CPAP</th>
<th>Mean (SD) MAD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysomnography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI, h⁻¹</td>
<td>4.5 (6.6)</td>
<td>11.1 (12.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ODI, %</td>
<td>6.0 (9.7)</td>
<td>9.0 (11.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Min SpO₂, %</td>
<td>90.6 (5.0)</td>
<td>87.2 (5.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SpO₂, TWD &amp; total sleep time</td>
<td>5.8 (16.9)</td>
<td>6.6 (15.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Arousal index, h⁻¹</td>
<td>16.6 (10.6)</td>
<td>19.2 (11.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>11.5 (15.7)</td>
<td>15.3 (21.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>82 (12)</td>
<td>82 (12)</td>
<td>0.9</td>
</tr>
<tr>
<td>Diary data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subj compliance, h/night</td>
<td>5.2 (2.0)</td>
<td>6.5 (1.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subj sleep, h/night</td>
<td>6.9 (0.9)</td>
<td>7.1 (0.7)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

• CPAP: 10.5±2 hPa (range 4–18 hPa)
• MAD: 8.09±2.6 mm (range 1.1–15 mm)
Obj/subj compliance CPAP: 4.68±2 / 5.1±2 (P<0.001)
Treatment preference:
51% MAD; 23% CPAP; 21% either; 5% neither
**II Sleep-disordered breathing**

**CPAP vs MAD**

**PSG outcomes:**

- Overall, BP was not lowered
- No differences CPAP/MAD:
  - 24MAP (Δ 0.2 [-0.7 to 1.1] mm Hg)
  - Other BP measures
- In subgroup of pts with initial hypertension, a consistent treatment related 24h BP decrease (2-4 mm Hg) was found; neither treatment was superior
- Their was a trivial decrease of arterial stiffness (1-2%)

*No striking differences in neurobehavioural outcomes were found*
Discussion:

- Largest and most complete RCT so far comparing CPAP/MAD
- Innovative design, esp. ‘acclimatization’ phase
- Focus group: moderate to severe OSA
- Confirmation of what is already known:
  - CPAP is better in terms of AHI reduction
  - MAD is superior regarding self-reported compliance and patient’s preference
- New: QoL is equivalent or better with MAD

Discussion: strengths

- The current study controls for weaknesses of previous trials:
  - exclusion of severe OSA (3 trials)
  - small sample sizes (<50 pts) (5 trials)
  - high dropout rates (>20%) (2 trials)
  - nonadjustable MAD (1 trial)
  - suboptimal compliance with CPAP (<4 h) (1 trial)
  - including acclimatization in the treatment period
- Power of the study
- Randomisation to avoid treatment expectation bias
II Sleep-disordered breathing

CPAP vs MAD

Discussion: limitations
• 20% (actually 25%) not eligible for MAD treatment
• No objective measures of MAD compliance (results adjusted)
• Some pts did not use CPAP or MAD during PSG evaluation
• Noninferiority cannot be claimed:
  – No effect from both treatment options on primary outcome BP
  – Most pts were normotensive

CPAP vs MAD

Discussion: limitations
• Noninferiority studies are appropriate when one treatment option would be clearly preferrable to another with similar effectiveness; this is not the case in CPAP vs MAD choice
  – personal preference is highly variable
  – MAD must be custom made
• It was NOT mathematically assessed to what extent “suboptimal efficacy with MAD is counterbalanced by better compliance relative to CPAP”
• Therefore, CPAP remains treatment of first choice
II Sleep-disordered breathing

HGN stimulation

Rationale and design:
- CPAP is effective for treatment of moderate-to-severe OSA, but insufficient compliance is an issue
- In this single-cohort study, a device (Inspire MS) for HGNS was implanted in 126 OSA pts, non-adherent to CPAP, (multi-center [22] single group cohort)
- Aim: to assess clinical safety and effectiveness @1 yr
- Primary outcomes: AHI, ODI and surgical criterion for treatment success (reduction of AHI > 50% and < 20)
- Secondary outcomes: ESS and FOSQ
**Exclusion criteria:**

- BMI > 32 kg/m²
- AHI < 20 or > 50/h (also >25% CSA or non-supine AHI < 10/h)
- ENT: pronounced anatomic abnormalities or highly collapsible airway (concentric collapse @ DISE)
- Neuromuscular disease (incl. HGN palsy)
- Cardiovascular and lung disease
- Active psychiatric disease / other sleep disorders

**Control:**

- RCT withdrawal study in 46 pt
- 1 week stop of treatment after 12 months
- Reassessment of primary outcomes
II Sleep-disordered breathing

HGN stimulation

Results:
• N = 126, 83% men, 55 yrs, BMI 28 kg/m², 38% AHT, 17% UPPP
• AHI: 32 → 15/h (P<.001)
• ODI: 30 → 14/h (P<.001)
• 43 (32%) failure, 83 (68%) had AHI <20/h, 67 (53%) <10/h and 37 (29%) < 5/h
• ESS: 12 → 7 (P<.001)
• FOSQ: 17 → 17 (P<.001)
• SAE: re-intervention in 2, other complications in 33
• Other AE: 23 temporary tongue weakness and 26 sore tongue

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Conclusions:
• In this uncontrolled cohort study, HGNS led to significant improvements in objective and subjective measures of the severity of OSA.
• Remaining issues:
  – Limited eligibility (BMI < 32 kg/m²; AHI < 50/h)
  – Definition of therapeutic success (in only 30% AHI score < 5/h is reached
  – Better identification of responders
  – Long-term effects of HGNS?
Implications for clinical practice

- The study of pathophysiology may be important to assess the ‘phenotype’ of OSA (yet, noninvasive methods will be needed)
- Pts with severe OSA may be at risk for incident AHT; those with resistant AHT may benefit from CPAP, but adherence to treatment is important
- Further news on OSA-cancer relationship is awaited
- It has not been proven that treatment with MAD is non-inferior to CPAP regarding blood pressure and other outcomes
- Although HGNS improves severity of OSA, a ‘cure’ is obtained in only a minority of patients
- Exclusion criteria limit applicability of MAD and HGNS
- AHI is losing importance in favour of ODI and HO-I