ΔΥΣΚΟΛΑ ΘΕΡΑΠΕΥΟΜΕΝΗ ΥΠΕΡΤΑΣΗ
ΤΑ ΥΠΝΙΚΑ ΑΠΝΟΙΑ

Αλέξανδρος Κασιακόγιας, MD, PhD
Clinical fellow
St George’s University of London
SLEEP APNEA AND HYPERTENSION
An association being studied for 40 years

OSA AS A CAUSE OF HTN?

PROSPECTIVE DATA

NO

NO

SHHS

Vittorio

YES

YES

Wisconsin

Zaragosa

Peppard PE. NEJM 2000
Marin JM. JAMA 2012

O’ Connor GT. AJRCCM 2009
Cano-Pumarega I. AJRCCM 2011
ZARAGOZA SLEEP COHORT
An observational prevention study

1889 patients without HT undergoing PSG
12.2 years of follow-up
Endpoint: HT incidence
Covariates included BMI changes

Adjusted HR for incident HT compared to controls without OSA:

Patients with OSA ineligible for CPAP therapy (1.33; 95% CI, 1.01-1.75)
Patients who declined CPAP therapy (1.96; 95% CI, 1.44-2.66)
Patients non-adherent to CPAP therapy (1.78; 95% CI, 1.23-2.58)
Patients with OSA who were treated with CPAP therapy (0.71; 95% CI, 0.53-0.94)

Marin JM et al. JAMA 2012
OSA AND HTN NUMBERS ARE CLEAR

General
- 6-20% (men)
- 6-9% (women)

HTN
- 40%

RHTN
- 71-90%

**OSA AND RESISTANT HYPERTENSION: ALL OVER THE PLACE**

**Screen for Secondary Causes of Hypertension**
- Obstructive sleep apnea (snoring, witnessed apnea, excessive daytime sleepiness)
- Primary aldosteronism (elevated aldosterone/renin ratio)
- Chronic kidney disease (creatinine clearance <30 ml/min)
- Renal artery stenosis (young female, known atherosclerotic disease, worsening renal function)
- Pheochromocytoma (episodic hypertension, palpitations, diaphoresis, headache)
- Cushing’s syndrome (moon facies, central obesity, abdominal striae, inter-scapular fat deposition)
- Aortic coarctation (differential in brachial or femoral pulses, systolic bruit)

**Pharmacologic Treatment**
Maximize diuretic therapy, including possible addition of mineralocorticoid receptor antagonist

**White-coat Effect**
- **Patient Management Issues**
  - Incorrect blood pressure measurement
  - Physician inertia
  - Inappropriate drug regimen
  - Insufficient drug doses

- **Adherence Issues**
  - Complicated regimen and dosing
  - Financial issues
  - Drug side effects
  - Lack of disease perception
  - Insufficient patient education

- **Secondary Hypertension**
  - Renal parenchymal disease
  - Renal artery stenosis
  - Primary hyperaldosteronism
  - Thyroid disease
  - Cushing’s syndrome
  - Pheochromocytoma
  - Aortic coarctation

- **Conditions Affecting Blood Pressure Control**
  - **Obstructive sleep apnoea**
  - Chronic kidney disease
  - Significant obesity
  - High salt intake
  - High alcohol consumption

**Drug-induced Resistant Hypertension**

---

Calhoun D et al. Hypertension 2008
Multicentre
Cross-sectional
ABPM
RHTN: 187
RfHTN: 42

Patients with RfHTN vs RHTN:

OR for
✓ Severe OSA: 2.1
✓ OSAS: 1.9

Martínez-García et al. Hypertension 2018
HOW TO MANAGE?

Follow the steps…
STEP 1:
REVIEW PATHOPHYSIOLOGY
ΥΠΝΙΚΗ ΑΠΝΟΙΑ ΚΑΙ ΥΠΕΡΤΑΣΗ
Παθοφυσιολογία

ΑΠΟΦΡΑΚΤΙΚΗ ΥΠΝΙΚΗ ΑΠΝΟΙΑ
Άπνοιες και υπόπνοιες

- Διαλείπουσα υποξία
- Υποτροπία ζουσες αφυπνίσεις
- Μεταβολές ενδοθωρακικής πίεσης

Συστηματική φλεγμονή
↑ Οξειδωτικό stress
↑ Ενδοθηλίνη

- Ενδοεσθητική δυσλείτουργία
- Ενεργοποίηση άξονα περίνη-αγγειοσινης - αλδοστερόνης

- Ενεργοποίηση αναδιαμόρφωση
↑ Αρτηριακή σκληρία

Α. Κασιακόγιας, Κ. Τσιούφης,....Χ. Στεφανάδης. Αρτηριακή Υπέρταση 2013.
Obstructive sleep apnoea
it’s all a matter of tension

UA open

UA occluded

✓ ↑ Oxygen demand
✓ LV Hypertrophy
✓ LV Dilatation
✓ Atrial Remodelling
✓ Aortic Dilatation

Floras J. Hypertension 2007
Kasai and Bradley. JACC 2011
Rostral Fluid Shift and the upper airway

HT begets HT through OSA?

- Application of lower body positive pressure leads to:
  - ↑ Neck circumference
  - ↓ Pharyngeal area
  - ↑ Pharyngeal collapsibility
- Fluid volume displaced from the legs overnight leads to an increase in OSA severity.
- This fluid volume is proportional to time spent sitting during the day/leg edema.
- In HF:
  - Fluid to pharynx…OSA
  - Fluid to lungs….CSA

Resistant HT

Sodium and water retention:

- Dietary
- SNS activation and renin release
- RAAS activation and increased aldosterone

Kasai T et al. Circulation 2012
ROSTRAL FLUID SHIFT AND OSA
Focus on resistant hypertension

Sodium and water retention:
- Dietary
- SNS activation and renin release
- RAAS activation and increased aldosterone

Rostral fluid shift
Worsening of OSA
Further BP increase
Resistant HT

The exaggerated fluid volume displacement from the legs and upper airway response to lower body positive pressure in patients with drug-resistant hypertension provide additional evidence of an important link between drug-resistant hypertension and obstructive sleep apnea.

Friedman O. Hypertension 2013
Conecny et al. Hypertension 2014
THE ROLE OF ALDOSTERONE

- 534 patients with RHTN
- AHI: 21.7 ± 9.6
- OSA: 92.3%

☑ PAC and 24 h-urine aldosterone levels were positively associated with AHI
☑ Spironolactone was negatively associated with AHI

Xiao Ke et al. Sci Rep 2017
STEP 2:

IDENTIFY TYPICAL BP PHENOTYPES
OSA AND HYPERTENSION

BP BEHAVIOUR

Diastolic HTN

Resistant HTN

Systolo-diastolic HTN

Masked HTN

NON-DIPPING
# 24ωρη Καταγράφη ΑΠ

## Overall Summary

<table>
<thead>
<tr>
<th></th>
<th>MIN</th>
<th>AVG</th>
<th>MAX</th>
<th>STD</th>
<th>Dipping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic:</td>
<td>102 (17:06 Mon)</td>
<td>138</td>
<td>180 (20:21 Mon)</td>
<td>14.26</td>
<td>2.2%</td>
</tr>
<tr>
<td>Diastolic:</td>
<td>67 (18:36 Mon)</td>
<td></td>
<td>91</td>
<td>122</td>
<td>-3.3%</td>
</tr>
<tr>
<td>MAP:</td>
<td>81</td>
<td>105</td>
<td>138</td>
<td>11.95</td>
<td>-1.9%</td>
</tr>
<tr>
<td>Pulse Pressure:</td>
<td>31</td>
<td>73</td>
<td>96</td>
<td>11.12</td>
<td></td>
</tr>
<tr>
<td>Heart Rate:</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Percent of Systolic above limits: 91.0%
Percent of Diastolic above limits: 78.2%

## Wake Period(s) 06:00 - 00:00

<table>
<thead>
<tr>
<th></th>
<th>MIN</th>
<th>AVG</th>
<th>MAX</th>
<th>STD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic:</td>
<td>102 (17:06 Mon)</td>
<td>139</td>
<td>180 (20:21 Mon)</td>
<td>15.91</td>
</tr>
<tr>
<td>Diastolic:</td>
<td>67 (18:36 Mon)</td>
<td></td>
<td>90</td>
<td>12.75</td>
</tr>
<tr>
<td>MAP:</td>
<td>81</td>
<td>104</td>
<td>138</td>
<td>12.92</td>
</tr>
<tr>
<td>Pulse Pressure:</td>
<td>31</td>
<td>49</td>
<td>109</td>
<td>10.59</td>
</tr>
<tr>
<td>Heart Rate:</td>
<td>53</td>
<td>71</td>
<td>96</td>
<td>11.15</td>
</tr>
</tbody>
</table>

Reading(s)      | Time        |
---              |---          |
91.0%           | 91.0%        |
78.2%           | 80.7%        |

Percent of Systolic readings > 120mmHg: 88.5%
Percent of Diastolic readings > 80mmHg: 73.8%

Number of Wake Period(s) readings: 61

## Sleep Period(s) 00:00 - 06:00

<table>
<thead>
<tr>
<th></th>
<th>MIN</th>
<th>AVG</th>
<th>MAX</th>
<th>STD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic:</td>
<td>127 (03:24 Tue)</td>
<td>136</td>
<td>145 (01:24 Tue)</td>
<td>5.27</td>
</tr>
<tr>
<td>Diastolic:</td>
<td>78 (01:51 Tue)</td>
<td></td>
<td>93</td>
<td>6.46</td>
</tr>
<tr>
<td>MAP:</td>
<td>96</td>
<td>106</td>
<td>119</td>
<td>7.12</td>
</tr>
<tr>
<td>Pulse Pressure:</td>
<td>33</td>
<td>44</td>
<td>58</td>
<td>7.31</td>
</tr>
<tr>
<td>Heart Rate:</td>
<td>70</td>
<td>79</td>
<td>92</td>
<td>6.62</td>
</tr>
</tbody>
</table>

Reading(s)      | Time        |
---              |---          |
100.0%          | 100.0%       |
94.1%           | 95.9%        |

Percent of Systolic readings > 120mmHg: 100.0%
Percent of Diastolic readings > 80mmHg: 94.1%

Number of Sleep Period(s) readings: 17
328 patients with OSA
Without antihypertensive treatment
Baseline evaluation: Dippers
Follow-up: 3-13 years

Table 3—The Association of Sleep-Disordered Breathing with Incidenta Systolic and Diastolic Nondipping Over an Average of 7.2-Year Follow-Up Period

<table>
<thead>
<tr>
<th>AHI Category</th>
<th>Total sample overall, no.</th>
<th>Incident nondipping, no. (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjustedb OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Nondipping (n = 220)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>162</td>
<td>22 (13.5)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>5 to &lt; 15</td>
<td>39</td>
<td>12 (30.8)</td>
<td>2.8 (1.3, 6.4)</td>
<td>3.1 (1.3, 7.7)</td>
</tr>
<tr>
<td>≥ 15</td>
<td>19</td>
<td>6 (33.3)</td>
<td>2.9 (1.0, 8.5)</td>
<td>4.4 (1.2, 16.3)</td>
</tr>
<tr>
<td>Diastolic Nondipping (n = 239)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>175</td>
<td>18 (10.3)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>5 to &lt; 15</td>
<td>43</td>
<td>9 (20.9)</td>
<td>2.3 (1.0, 5.6)</td>
<td>2.0 (0.7, 5.6)</td>
</tr>
<tr>
<td>≥ 15</td>
<td>21</td>
<td>3 (14.3)</td>
<td>1.5 (0.4, 5.4)</td>
<td>1.1 (0.2, 6.3)</td>
</tr>
</tbody>
</table>

Hla KM. Sleep 2008
STEP 3:

DON’T MISS THE DIAGNOSIS OF OSA
ASSESSING FOR SLEEP APNEA

EPWORTH

1. Διαβάζετε την επιγραφή στη σελίδα (0-3)
2. Προληπτικά και αποκλειστικά σε δημόσιο χώρο (π.χ. θέατρο ή συγκέντρωση)
3. Καθημερινή και συχνή σε δημόσιο χώρο (π.χ. θέατρο ή συγκέντρωση)
4. Επιμέλεια σε σεκκίνι για μια ώρα χωρίς στοχαιρίζει
5. Σημαντικό για το απόγευμα όταν η περιόδους του ξεπερνούν
6. Μιλάντας σε κάποιον καθημερινά(η)
7. Καθημερινά(ή) σε έναν ή περιβάλλον με το μεταβαμμένο χώρο να έχετε κατανοήσει ακόμη
8. Σε σεκκίνι για εννεά είπε πακιστάνι(η) για λίγα λεπτά λόγους κίνησης

Χρησιμοποιήστε την παρακάτω κλίμακα διαλέγοντας τον αριθμό που αντιστοιχίζεται σε σας σε κάθε περίπτωση:
0 = καμία περίπτωση να αποκομιδήθηκε
1 = ελάχιστη πειθαρχία να αποκομιδήθηκε
2 = μέτρια πειθαρχία να αποκομιδήθηκε
3 = μεγαλύτερη πειθαρχία να αποκομιδήθηκε

Επικοινωνία με τον υποψηφίο για το ερωτηματολόγιο

BERLIN

Ονοματεπώνυμο:
1. Όνομα: Άρωμα:
2. Άρωμα:
3. Όρος:
4. Φύλο:

Κατηγορία 1
7. Πόσο συχνά νιώθετε κουρασμένος/η μετά τον ύπνο σας:
✓ Σχεδόν καθέ μέρα
✓ 3-4 φορές την εβδομάδα
✓ 1-2 φορές την εβδομάδα
✓ Ποτέ ή σχεδόν ποτέ

Κατηγορία 2
8. Κατά τη διάρκεια της ημέρας, αυξάνεστε κουρασμένος/η ή ότι έχετε κουρασμένες λίγες ώρες:
✓ Σχεδόν καθέ μέρα
✓ 3-4 φορές την εβδομάδα
✓ 1-2 φορές την εβδομάδα
✓ Ποτέ ή σχεδόν ποτέ

Κατηγορία 3
9. Έχετε αποκομιθεί ποτέ ενώ οδηγούσατε:
✓ Ναι
✓ Όχι

Εννέα ή περισσότερες θετικές απαντήσεις στις κατηγορίες 1-6
Κατηγορία 2: θετική θέση 2 ή περισσότερες θετικές απαντήσεις στις κατηγορίες 3-6
Κατηγορία 3: θετική θέση 1 ή περισσότερες θετικές απαντήσεις και ή BMI 30

Εκτίμηση απρομηθευτικής απόπτωσης?
✓ Ναι
✓ Όχι

BMI:
BERLIN QUESTIONNAIRE IN OSA

- 442 patients with RHTN
- Berlin questionnaire
- Polysomnography

- Accuracy: 55.6%
- Specificity: 40%
- Sensitivity: 69%

Margallo VS et al. J Hypertens 2014
NECK CIRCUMFERENCE

- men: >43 cm
- women: >37 cm

THE UVULA

The Mallampati Score

CLASS I
Complete visualization of the soft palate

CLASS II
Complete visualization of the uvula

CLASS III
Visualization of only the base of the uvula

CLASS IV
Soft palate is not visible at all
## Portable monitoring devices

<table>
<thead>
<tr>
<th>Type 2</th>
<th>Comprehensive Portable (PSG at home)</th>
<th>Minimum of 7 channels, including EEG, EOG, chin EM, ECG or HR, airflow, respiratory effort, and SpO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 3</td>
<td>Modified Portable Sleep ApneaTesting (No sleep stages)</td>
<td>Minimum of 4 channels monitored, including ventilation or airflow (at least 2 channels of respiratory movement, or respiratory movement and airflow), heart rate or ECG and SpO2</td>
</tr>
<tr>
<td>Type 4</td>
<td>Continuous Single or Dual Bioparameters</td>
<td>One or 2 channels, typically including oxygen saturation or airflow</td>
</tr>
</tbody>
</table>

- For patients with high pretest probability for moderate-severe OSA
- For immobile, critically ill patients
- Not in comorbid conditions (e.g. COPD)
- Not for screening in general population
34,7/ώρα
STEP 4: TREAT OSA
Recommendation 1: We recommend that clinicians use positive airway pressure, compared to no therapy, to treat OSA in adults with excessive sleepiness. (STRONG)

Recommendation 3: We suggest that clinicians use positive airway pressure, compared to no therapy, to treat OSA in adults with comorbid hypertension. (CONDITIONAL)
Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares.

Sullivan CE, Issa FG, Berthon-Jones M, Eves L

Abstract
Five patients with severe obstructive sleep apnoea were treated with continuous positive airway pressure (CPAP) applied via a comfortable nose mask through the nares. Low levels of pressure (range 4.5-10 cm H2O) completely prevented upper airway occlusion during sleep in each patient and allowed an entire night of uninterrupted sleep. Continuous positive airway pressure applied in this manner provides a pneumatic splint for the nasopharyngeal airway and is a safe, simple treatment for the obstructive sleep apnoea syndrome.

PMID: 6112294 [PubMed - indexed for MEDLINE]
<table>
<thead>
<tr>
<th>Study</th>
<th>No of trials</th>
<th>N</th>
<th>BP measure</th>
<th>MBP 95% CI</th>
<th>SBP 95% CI</th>
<th>DBP 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazzano 2007</td>
<td>16</td>
<td>818</td>
<td>Manual ABPM</td>
<td>-2.22 -4.38 to 0.05</td>
<td>-2.46 -4.31 to -0.62</td>
<td>-1.83 -3.05 to -0.61</td>
</tr>
<tr>
<td>Haentjens 2007</td>
<td>12</td>
<td>572</td>
<td>ABPM</td>
<td>-1.69 -2.69 to -0.69</td>
<td>-1.77 -3.00 to -0.54</td>
<td>-1.79 -2.87 to -0.71</td>
</tr>
<tr>
<td>Alajmi 2007</td>
<td>10</td>
<td>587</td>
<td>Manual ABPM</td>
<td>-1.38 3.6 to -0.88</td>
<td>1.52 3.11 to -0.07</td>
<td></td>
</tr>
</tbody>
</table>

Subgroup Analysis-Predictors of BP decrease:
- AHI at entry
- BP at entry
- BMI
- Hours of use/night

<table>
<thead>
<tr>
<th>Author</th>
<th>No of studies</th>
<th>Patient No</th>
<th>BP Measure</th>
<th>Effect</th>
<th>Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montesi SB 2012</td>
<td>28</td>
<td>1948</td>
<td>Ambulatory</td>
<td>-2.58/-2.01</td>
<td>Younger age, Sleepiness, AHI, Adherence, Baseline BP</td>
</tr>
<tr>
<td>Fava C 2014</td>
<td>31</td>
<td>1820</td>
<td>Office Ambulatory</td>
<td>-2.6±0.6/2.0±0.4</td>
<td>Baseline AHI</td>
</tr>
<tr>
<td>Schein AO 2014</td>
<td>16</td>
<td>1166</td>
<td>Office Ambulatory</td>
<td>-3.20/2.87</td>
<td>-</td>
</tr>
<tr>
<td>Xinyu H 2015</td>
<td>7</td>
<td>794</td>
<td>Ambulatory</td>
<td>-2.32/1.98</td>
<td>Compliance, Age, Baseline SBP, RHT</td>
</tr>
</tbody>
</table>
Effects of continuous positive airway pressure on blood pressure in hypertensive patients with obstructive sleep apnea: a 3-year follow-up

Alexandros Kasiakogias, Costas Tsioufis, Costas Thomopoulos, Dimitrios Aragiannis, Manos Alchanatis, Dimitrios Tousoulis, Vasilios Papademetriou, John S. Floras, and Christodoulos Stefanadis

- 91 hypertensive patients with OSA (AHI>15)
- Without daytime sleepiness
- Acceptance vs refusal of CPAP
- CPAP was not associated with lower BP levels or fewer antihypertensive drugs needed for BP control

“...a recent study with a follow-up longer than 3 years has found no difference in BP or in drug usage between sleep apnoea patients who continued, or those who quitted positive air pressure therapy.”

ESH/ESC guidelines 2013
PREDICTORS OF BP RESPONSE TO CPAP

- OSA severity (usually based on AHI)?
- (Untreated-Uncontrolled) hypertension?
- Baseline BP levels?
- Daytime sleepiness?
- Adherence to CPAP and duration of night-time application
CPAP EFFECT ON BP IN RHTN

- Open label
- Multicentre
- Randomized
- 194 RHTN patients
- AHI>15
- Meds vs CPAP and meds

↓ 24-hour MBP (3.1mmHg [95%CI, 0.6 to 5.6]; \( P = .02 \))
↓ 24-hour DBP (3.2mmHg [95%CI, 1.0 to 5.4]; \( P = .005 \))
No effect on 24-hour SBP (3.1mmHg [95%CI, −0.6 to 6.7];

Martínez-García et al, JAMA 2013
Navarro-Soriano C et al. J Hypertens 2019
117 RHT patients
- Median 5 drugs (47% Spiro-)
- Moderate to severe OSA
- Mean AHI: 41/hr
- CPAP vs conventional treatment
- 6 month follow-up
- No significant effect on clinic and 24hr BP

CPAP treatment nonsignificantly decreased:
- 7% the odds of nondipping
- 43% of a riser pattern
- 27% the odds of having uncontrolled ambulatory BP levels

Effects of Continuous Positive Airway Pressure Treatment on Clinic and Ambulatory Blood Pressures in Patients With Obstructive Sleep Apnea and Resistant Hypertension: A Randomized Controlled Trial


Abstract—The effect of continuous positive airway pressure (CPAP) on blood pressures (BPs) in patients with resistant hypertension and obstructive sleep apnea is not established. We aimed to evaluate it in a randomized controlled clinical trial, with blinded assessment of outcomes. Four hundred thirty-four resistant hypertensive patients were screened and 117 patients with moderate/severe obstructive sleep apnea, defined by an apnea–hypopnea index ≥15 per hour, were randomized to 6-month CPAP treatment (57 patients) or no therapy (60 patients), while maintaining antihypertensive treatment. Clinic and 24-hour ambulatory BPs were obtained before and after 6-month treatment. Primary outcomes were changes in clinic and ambulatory BPs and in nocturnal BP fall patterns. Intention-to treat and per-protocol (limited to those with controlled ambulatory BP) analyses were performed. Patients had mean (SD) 24-hour BP of 129 (16)/75 (12) mm Hg, and 2 obstructive sleep apnea and an increase in nocturnal BP in per-protocol analysis with a control group resistant hypertension.

<table>
<thead>
<tr>
<th>Blood Pressures</th>
<th>Mean (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BPs, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>-6.1 (-17.5 to +5.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>24 h</td>
<td>-3.2 (-9.3 to +2.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Daytime</td>
<td>-1.4 (-7.6 to +4.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>Night-time</td>
<td>-4.7 (-11.3 to +3.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Nocturnal fall (%)</td>
<td>2.2 (-1.6 to +5.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diastolic BPs, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>-1.1 (-8.7 to +6.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>24 h</td>
<td>-1.9 (-6.1 to +2.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Daytime</td>
<td>-1.6 (-6.0 to +2.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Night-time</td>
<td>-1.0 (-5.9 to +3.9)</td>
<td>0.69</td>
</tr>
<tr>
<td>Nocturnal fall (%)</td>
<td>0.2 (-4.4 to +4.7)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Muxfeldt E et al. Hypertension 2015
In randomized controlled studies (n=309 patients), there was a reduction during follow up in 24-h mean SBP of −3.9 mm Hg and in 24-h mean DBP of −3.5 mm Hg with CPAP versus medical therapy.

Treatment

Conservative measures

- Avoid sedatives
- Avoid alcohol
- Stop smoking
- Weight loss
- Increase sleep time
- Avoid supine posture
Oral appliance devices (Mandibular advancement device)

- Primary snoring
- Intolerance to CPAP
- Patient preference
- Needs a dentist

AASM. J Clin Sleep Med 2015
STEP 5:

CHOOSE YOUR DRUG
## CHOOSING THE RIGHT DRUG IN OSA?

<table>
<thead>
<tr>
<th>Study design</th>
<th>n</th>
<th>CPAP (Y/N)</th>
<th>AHDs: dosage (mg/day)</th>
<th>BP measurement</th>
<th>BP outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT, double-blinded, balanced</td>
<td>40</td>
<td>No</td>
<td>Atenolol (60); amiodipine (6); enalapril (20); hydrochlorothiazide (25); losartan (30)</td>
<td>Office EP 24h ABPM</td>
<td>↓ in office SBP and daytime ABPM NS for all drugs; Atenolol ↓ night-time 24 h SBP and DBP more effectively than amiodipine, enalapril or losartan</td>
<td>Karači et al., 2000</td>
</tr>
<tr>
<td>incomplete block design (6 w each drug + 3 w washout)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT, double-blinded; crossover schedule</td>
<td>15</td>
<td>No</td>
<td>Atenolol (60); isradipine (2.5); hydrochlorothiazide (25); spironol (6)</td>
<td>Office EP</td>
<td>Slight ↓ BP for all drugs; Only enalapril affected BP variability</td>
<td>Sito et al., 1999</td>
</tr>
<tr>
<td>(6 w each drug + 2-3 w washout)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT, double-blinded; crossover</td>
<td>18</td>
<td>NA</td>
<td>Atenolol (60); isradipine (2.5); hydrochlorothiazide (25); spironol (6)</td>
<td>24 h ABPM</td>
<td>↓ mean 24 h SBP (except for HCTZ) ↓ mean 24 h DBP (for all drugs) NS ↓ mean night-time SBP and DBP (for all drugs)</td>
<td>Pollart et al., 1999</td>
</tr>
<tr>
<td>(6 w each drug + 2-3 w washout)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT (3 months each treatment)</td>
<td>75</td>
<td>Yes</td>
<td>Treatment with at least 3 drugs at adequate doses, including a diuretic</td>
<td>24 h ABPM</td>
<td>CPAP + AHDs regimen ↓ 4.9 mmHg 24 h DBP; AHDS regimen alone NS</td>
<td>Lozano et al., 2010</td>
</tr>
<tr>
<td>RCT, single-blinded (3 w each regimen)</td>
<td>44</td>
<td>Yes</td>
<td>Valsartan (150) + amiodipine (5-10) + hydrochlorothiazide (25)</td>
<td>Office EP 24h ABPM</td>
<td>AHDS alone; ↓ office and 24 h SBP and DBP Additional ↓ in office BP and ambulatory BP monitoring (CPAP + 3 AHDS)</td>
<td>Livin et al., 2013</td>
</tr>
<tr>
<td>RCT, crossover (6 w each treatment + 4 w washout)</td>
<td>23</td>
<td>Yes</td>
<td>Valsartan (150)</td>
<td>Office EP 24h ABPM</td>
<td>CPAP: ↓ 2.1 mmHg 24 MBP and ↓ 1.3 mmHg night-time MBP (NS) VALS: ↓ 9.1 mmHg 24 MBP and ↓ 6.1 mmHg night-time MBP</td>
<td>Pinel et al., 2009</td>
</tr>
<tr>
<td>RCT (8 w)</td>
<td>12</td>
<td>No</td>
<td>Spironolactone (25-50) added to current medication (mean number of AHDs: 4.3 (SD = 1.1)</td>
<td>Office EP 24h ABPM</td>
<td>↓ 17 mmHg 24 h SBP ↓ 10 mmHg 24 h DBP</td>
<td>Gaddam et al., 2010</td>
</tr>
<tr>
<td>RCT, double-blind (8 days)</td>
<td>12</td>
<td>NA</td>
<td>Metoprolol (100); cilazapril (2.5)</td>
<td>Office EP 24h ABPM</td>
<td>MET ↓ 13 mmHg 24 h SBP and ↓ 5 mmHg 24 h DBP CIL: ↓ 13 mmHg 24 h SBP and ↓ 17 mmHg 24 h DBP</td>
<td>Mayer et al., 1990</td>
</tr>
<tr>
<td>RCT, double-blind; crossover</td>
<td>16</td>
<td>No</td>
<td>Doxazosin (4-8); enalapril (10-20)</td>
<td>24 h ABPM</td>
<td>DOX: ↓ 4.1 mmHg 24 h SBP and ↓ 5.1 mmHg 24 h DBP EN: ↓ 12.6 mmHg 24 h SBP and ↓ 8.9 mmHg 24 h DBP 24 h MBP: no differences between groups</td>
<td>Zou et al., 2010</td>
</tr>
<tr>
<td>(2 w each treatment + 3 w washout)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT, double-blind, parallel group,</td>
<td>31</td>
<td>No</td>
<td>Nebivolol (8); valsartan (80)</td>
<td>Office EP</td>
<td>NEB: ↓ 14.6 mmHg SBP and ↓ 8.6 mmHg DBP VALS: ↓ 11.6 mmHg SBP and ↓ 8.9 mmHg DBP No differences between treatments</td>
<td>Hoffmann et al., 2010</td>
</tr>
<tr>
<td>single center (6 w)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diogo LN. F Physiol 2014
TARGETING THE SYMPATHETIC NERVOUS SYSTEM

<table>
<thead>
<tr>
<th>Pro</th>
<th>Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNS activation is a primer effect</td>
<td>Fear of nighttime bradyarrhythmias</td>
</tr>
<tr>
<td>May improve HR variability</td>
<td>Functional downregulation of vascular adrenergic receptors</td>
</tr>
</tbody>
</table>

- **Pro**
  - SNS activation is a primer effect
  - May improve HR variability

- **Against**
  - Fear of nighttime bradyarrhythmias
  - Functional downregulation of vascular adrenergic receptors
TARGETING THE RAAS

SNS activation
Hyperinsulinemia
BNP triggered diuresis
Obesity

Interaction of ACE insertion/deletion polymorphisms with OSA is associated with hypertension

Aldosterone is increased and associated with OSA severity at least in resistant hypertension patients

Very limited data

ACEI may exacerbate OSA through pharyngeal inflammation
Aldosterone antagonists reduced AHI by 21.12 (95% CI: -27.47 to -14.77)

Zhang WD et al. J Hum Hypertens 2017
16 patients with uncontrolled HT (2.9±1.4 drugs) and OSA (AHI>20/hr)

- Metolazone and spironolactone for 14 days

- Significant reduction in AHI (from 57.7 to 48.5/hr)
- Significant reduction in Leg Fluid Volume that correlated with changes in BP during polysomnography

Kasai T et al. J Hypertens 2014
41 patients with hypertension and OSA (AHI>15/hr) without daytime sleepiness

Prospective cross-over trial

Valsartan or Valsartan/Amlodipine dosing in the morning vs evening

Evening compared to morning dosing was accompanied by:

✓ Similar 24hr BP decreases
✓ Greater night time BP decrease
✓ More patients turning to dippers

TREATING A PATIENT WITH OSA AND HYPERTENSION

**Rule No 1:** Follow the general ESH/ESC Guidelines

**Rule No 2:** Apply CPAP when appropriate (or other OSA options)

**Rule No 3:** Follow the general ESH/ESC Guidelines.

DON’T FORGET WEIGHT LOSS
The aim of this study was to identify plasma miRNA profiles that predict blood pressure responses to CPAP treatment.

✓ A singular pre-CPAP treatment cluster of 3 plasma miRNAs predicts blood pressure responses to CPAP treatment in patients with RHTN and OSA.

✓ CPAP treatment is accompanied by changes in cardiovascular system–related miRNAs that may potentially influence the risk for cardiovascular disease among patients with OSA and RHTN.

Sánchez-de-la-Torre M. JACC 2015
CONCLUSIONS

• There is a widely studied association between OSA and BP that may be bidirectional, and should be considered in the context of the multifactorial pathophysiology of both conditions.
• CPAP has an acute positive effect on BP behaviour alleviating the sudden post-apnoeic BP increases, that cannot be registered with conventional intermittent BP monitoring.
• CPAP application may modestly decrease average BP in selected patient groups, but the overall effect is small, and not easily identified on top of antihypertensive treatment.
• All classes of antihypertensive drugs can be used as initial or combination treatment following current guidelines, and further considering any beneficial effects with respect to OSA severity.
ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ