Dr. Javaheri has received research grants from Respironics and participates in Respironics’ and ResMed’s Speaker’s Bureau, but these do not create a conflict related to the following presentation.
Positive Airway Pressure Treatment for Obstructive Sleep Apnea and Central Sleep Apnea in Heart Failure

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3/20/2013
Learning objectives

- 50% of HF patients, both HFREF and HFPEF, have SA.
- SA, both OSA and CSA, is associated with mortality (HR=2)
- OSA is easily suppressed by CPAP
- CSA is suppressed by CPAP in 50% of the patients
- ASV is recommended in CPAP non-responders
- Effective treatment of SA improves mortality
Train of OSA

Polysomnography - 5 minutes page
Prevalence of sleep apnea in Systolic Heart Failure

100 out of 114 consecutive patients
10% on beta blockers

Javaheri et al:

*Ann Intern Med* 1995
*Circulation* 1998
*Int J Cardiol* 2006

AHI $\geq 15$/h 49%
## Prevalence of sleep apnea (AHI≥15/h) in recent prospective studies of HFrEF

<table>
<thead>
<tr>
<th>Country (year)</th>
<th>n</th>
<th>% AHI≥15/hr</th>
<th>% CSA</th>
<th>% OSA</th>
<th>% β blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>*USA (06) Javaheri</td>
<td>100</td>
<td>49</td>
<td>37</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>USA (08) Mcdonald</td>
<td>108</td>
<td>61</td>
<td>31</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>*Canada (07) Wang</td>
<td>287</td>
<td>47</td>
<td>21</td>
<td>26</td>
<td>80</td>
</tr>
<tr>
<td>*UK (07) Vazir</td>
<td>55</td>
<td>53</td>
<td>38</td>
<td>15</td>
<td>78</td>
</tr>
<tr>
<td>Germany (07) Oldenberg</td>
<td>700</td>
<td>52</td>
<td>33</td>
<td>19</td>
<td>85</td>
</tr>
<tr>
<td>*Germany (09) Hagenda</td>
<td>50</td>
<td>64</td>
<td>44</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>*Germany (10) Jilek</td>
<td>273</td>
<td>64</td>
<td>50</td>
<td>14</td>
<td>88</td>
</tr>
<tr>
<td>*Portugal (10) Ferreira</td>
<td>103</td>
<td>46</td>
<td>n/a</td>
<td>n/a</td>
<td>90</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1676</td>
<td>54</td>
<td>34</td>
<td>20</td>
<td>81</td>
</tr>
</tbody>
</table>
Prevalence of sleep apnea (AHI≥15) in consecutive patients with HFrEF

- AHI≥15/hr: 54% (897/1676)
- CSA: 34% (541/1573)
- OSA: 20% (308/1573)
Prevalence of Sleep Apnea in HFpEF (n=244), Bitter, EJHF 2009

AHI≥15/hr

- Total: 48%
- OSA: 25%
- CSA: 23%
Worldwide prevalence of sleep apnea in HF consecutive patients

- AHI ≥ 15
  - Low EF (n=1250): 52%
  - Normal EF (n=244): 48%

- CSA
  - Low EF: 31%
  - Normal EF: 23%

- OSA
  - Low EF: 21%
  - Normal EF: 25%
Prevalence of sleep apnea in heart failure

AHI $\geq 15/h$

9% of men in general population have AHI $\geq 15/h$
50% of consecutive patients with HF have AHI $\geq 15/h$

HF is the most common risk factor for moderate to severe sleep apnea
Introduction of beta blockers to treat heart failure has resulted in a significant decrease in prevalence of sleep apnea in CHF.

Heart failure patients with sleep apnea commonly suffer from EDS when compared to heart failure patients without sleep apnea.

The prevalence of sleep apnea is higher in patients HFpEF compared with HFrEF.

In heart failure, the length of a cycle of periodic breathing correlates with circulation time (correct answer).
Under-diagnosis of sleep apnea in heart failure

A retrospective cohort study used the 2004-2005 Medicare Standard Analytical Files (SAFs).

SAFs contain a 5% sample of randomly selected Medicare beneficiaries.

The study population included newly diagnosed HF patients in the first quarter of 2004 without prior diagnosis of SA.
Under-diagnosis of sleep apnea in patients with heart failure

Study Cohort
N=30,719

SA tested
N=572 (2%)

Not SA tested
N=30,147 (98%)

Javaheri et al. Am J Respir Crit Care Med 2011
Under-diagnosis of sleep apnea in patients with heart failure

Study Cohort
N=30,719

SA tested
N=572 (2%)

Not SA tested
N=30,147 (98%)

SA Dx: N=553 (97%)

No SA Dx N=19 (3%)

Javaheri et al. Am J Respir Crit Care Med 2011
Why Sleep apnea is under-diagnosed in patients with heart failure?

The mystery

*lack of perceived EDS*

in patients with HF with SA
No difference in subjective EDS among the 3 groups HFrEF (n=100)

No SA  CSA  OSA

p=0.8

No difference in subjective EDS among the 3 groups HFrEF (n=100)

AHI, n/hr

No SA  CSA  OSA

2  48  32
Epworth Sleepiness Scale

Using the following scale, circle the most appropriate number for each situation.

0 = would doze less than once a month
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dozing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Watching TV</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Sitting, inactive in a public place (in a theater or in a meeting)</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon (when circumstances permit)</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in the traffic</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

Add the 8 numbers you have circled ___________________________________
Clinical impact of lack of subjective EDS in HF

Under diagnosis of sleep apnea in HF

Poor adherence to therapy
The reason why cardiologists do not commonly refer HF patients for PSG is:

1. Heart failure patients with sleep apnea commonly do not complain of EDS
2. The prevalence of sleep apnea has decreased with the use of beta blockers
3. Minimal involvement of cardiologists in various aspects of sleep apnea diagnosis and treatment
4. Lack of education
5. 1, 3, and 4 (correct answer)
Biological pathways mediating CV complications of sleep apnea
Javaheri, Principles and Practice of Sleep Medicine, 2011

- \( \downarrow \text{O}_2 \) delivery → Organ dysfunction
- Oxidative stress Inflammation → Endothelial dysfunction
  - Hypoxic and hypercapnic pulmonary vasoconstriction → Right ventricular afterload
  - Sympathetic activation → Blood pressure Arrhythmias Myocyte toxicity
    - Parasympathetic withdrawal → Heart rate
      - Transmural pressure of all cardiac chambers Aorta Pulmonary capillary hydrostatic pressure → R and L ventricular afterload Arrhythmias (atrial)
        - Increased lung H2O
- \( \uparrow \text{PO}_2 / \downarrow \text{PCO}_2 \)
- \( \uparrow \text{PO}_2 / \downarrow \text{PCO}_2 \)
- Arousals
- \( \downarrow \text{Pleural Pressure} \)
Long-term adverse CV consequences

Neurohormonal stimulation
  Increased sympathetic activity, endothelin, BNP, EP

Oxidative stress

Inflammation

Decreased LVEF

Arrhythmias

Increased mortality. Treatment matters?
Treatment of OSA in HF

Optimization of CV function
Promotion of sleep hygiene
Avoid ETOH, benzodiazepines, opioids, and Viagra
Cessation of smoking
Weight loss (yes or no?)

**PAP devices: CPAP**, bilevel, positive end-expiratory P(Provent)
Negative intraoral pressure device (Winx)
Positional therapy
Mandibular advancement devices
Upper airway procedures (e.g. UPPP)
Hypoglossal nerve stimulation
Nocturnal use of supplemental oxygen
1. Heart failure patients with obstructive sleep apnea are best treated with an ASV device.

2. RCT have shown improved survival of heart failure patients with OSA when treated with CPAP compared with those on sham CPAP or a control group.

3. In contrast to OSA in general population, OSA in heart failure is not easily suppressed by CPAP.

4. Observational studies in patients with heart failure and OSA, show that CPAP compliance improves survival (correct answer).
Only RCT can prove causality
KM analysis of mortality–transplant among CHF patients untreated for SDB

Outcome depending on SDB pattern in CHF

NoSDB; AHI < 5.0 h⁻¹ (N=50)

OSA with AHI ≥ 5.0 h⁻¹ (N=236)

CSA with AHI ≥ 5.0 h⁻¹ (N=98)

Chi-square log-Rank test = 11.9, p=0.003

Months

Follow-up

Damy et al., Eur J Heart Fail 2012
Cumulative event-free survival in CPAP-treated and untreated patients

N=65, 59% on β blocker
AHI: 45 /hr
LVEF: 36%

N=23, 61% on β blocker
AHI: 38 /hr
LVEF: 35%

HR 2.03 (1.07-3.68) P=0.03

Cumulative event-free survival by compliance status

- (6.0 hr/night)
- (3.5 hr/night)

HR 4.02 (1.33-12.2) P=0.014

N=32
AHI: 46/hr
LVEF: 37%

N=33
AHI: 44/hr
LVEF: 35%

Under-diagnosis of sleep apnea in patients with heart failure

Study Cohort
N=30,719

SA tested
N=572 (2%)

SA Dx: N=553 (97%)
- tested, diagnosed, not treated
  N=295
- tested, diagnosed, treated
  N=258

Not SA tested
N=30,147 (98%)

No SA Dx N=19 (3%)

Javaheri et al. Am J Respir Crit Care Med 2011
Kaplan-Meier Survival Curves, Adjusted by Age, Gender, and Charlson Comorbidity Index, 2004-2005

Percent of Cohort Alive

Baseline 1 2 3 4 5 6 7 8

Hazard ratio = .33 (95% CI = .21-.51), P < .0001

- 258 HF patients Tested, diagnosed with sleep apnea, and treated
- 30,065 HF patients Not tested and not treated for sleep apnea
Kaplan-Meier Survival Curves, Adjusted by Age, Gender, and Charlson Comorbidity Index, 2004-2005

Tested, Diagnosed and Treated
N=258

Tested, Diagnosed and Not treated
N=295

Hazard ratio = .49 (95% CI = .29-.84), P=0.009

Javaheri et al. Am J Respir Crit Care Med 2011
## 2 y hospitalizations, cost and all cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Tested, diagnosed</th>
<th>Clinically suspected not treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No (%)</td>
<td>258 (100)</td>
<td>630 (100)</td>
</tr>
<tr>
<td>Mortality, No (%)</td>
<td>20 (7.8)</td>
<td>185 (29.4)</td>
</tr>
<tr>
<td>Patients hospitalized, No (%)</td>
<td>192 (74)</td>
<td>570 (91)</td>
</tr>
<tr>
<td>Medicare payment per patient</td>
<td>42859 $</td>
<td>63747 $</td>
</tr>
<tr>
<td>Difference per patient</td>
<td>21000 $</td>
<td></td>
</tr>
</tbody>
</table>
Medicare savings

If 630 patients were all tested, diagnosed and treated with CPAP:

Cost of 2 sleep studies 1300 $
Cost of CPAP device 1200 $
Cost per patient 2500 $
Cost for 630 patients 1,6 million $
Actual cost difference for 630 patients 13,200000 $
2 y Medicare savings for 630 patients 12 million $
CSA is an independent predictor of mortality in SHF

- N = 114 eligible
- N = 100 Enrolled
- N = 12 with OSA Excluded
- N = 88
  - 32 with AHI <5/hr (mean = 2)
  - 56 with AHI ≥5/hr (mean = 34; CAI = 23)
- Median F/U: 51 months

Javaheri et al, J Am Coll Cardiol (May, 2007)
CSA is a Predictor of Mortality in SHF

AHI < 5/h, mean = 2, n=32
AHI ≥5/h mean = 34, CAI = 23, n=56

Survival %

Hazard ratio=2.14
P=0.02

The predictors of poor survival in SHF

Three variables, AHI, RVEF and DBP independently correlated with poor survival:

- AHI   (HR=2.14, P=0.02)
- RVEF  (HR=0.97, P=0.003)
- DBP   (HR=0.96, P=0.02)

Javaheri, JACC, 2007
1. In heart failure central sleep apnea is commonly suppressed with CPAP.

2. The post hoc analysis of the Canadian CPAP trial has shown improved survival of heart failure patients whose CSA was suppressed with CPAP when compared with sham CPAP.

3. Multiple studies have shown that CSA is an independent predictor of survival in HF and that effective treatment improves survival. (correct)

4. RCT have shown that ASV devices improve survival of HF patients with CSA.
Treatment of sleep apnea with CPAP in SHF

In regard to therapy with CPAP, how does CSA differ from OSA?
## CSA in SHF

**Prevalence of CPAP-responders and non-responders**

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21</td>
<td>43%</td>
<td>57%</td>
</tr>
</tbody>
</table>

AHI(36 to 4/h)    AHI(62 to 62)

Javaheri, Circulation, 2000
CPAP=6cm with Flex 3
Heart-Transplantation-Free Survival

CPAP group, n=128

Control group

P=0.54

Bradley TD et al., *N Engl J Med* 2005
Potential mechanisms of CPAP failure

1. CPAP- nonresponders (43 % up to 57%)
2. Adverse hemodynamic consequences of CPAP:
   CPAP increases intrathoracic P and decreases venous return to R ventricle

Javaheri, JCSM, 2006
Potential mechanisms of CPAP failure

Adverse hemodynamic consequences of CPAP:
CPAP decreases RV stroke volume, LV stroke volume, BP and CBF.

Hemodynamic effects of atrial fibrillation

Javaheri, JCSM, 2006
The predictors of poor survival in SHF

Three variables, AHI, RVEF and DBP independently correlated with poor survival:

- AHI: HR=2.14, P=0.02
- RVEF: HR=0.97, P=0.003
- DBP: HR=0.96, P=0.02

Javaheri, JACC, 2007
Transplant-free survival in SHF patients according to effect of CPAP on CSA (Artz, Circ, 2007)

CPAP responders, AHI = 6.5
n = 57, β blocker, 81%

Control, AHI = 36
n=130
β blocker, 78%

* vs. control: HR=0.36, p=0.040
Transplant-free survival in the control group and according to effect of CPAP on CSA

**CPAP responders, n = 57**
AHI at 3 months < 15/hr, mean=6.5

**CPAP non-responders, n = 43**
AHI at 3 months ≥ 15/hr, mean=35

Control, n = 110
AHI at 3 months ≥ 15/hr, mean=36

*versus control: HR=0.36, p=0.040*
### CSA in SHF

#### Prevalence of CPAP-responders and non-responders

**Potential Therapeutic Role of PSSV Devices**

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Javaheri (1\textsuperscript{st} night)</td>
<td>21</td>
<td>43% AHI (36 to 4/h)</td>
<td>57% AHI (62 to 62), (lowPCO\textsubscript{2})</td>
</tr>
<tr>
<td>(Circulation, 2000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artz (at 3 m)</td>
<td>100</td>
<td>57% AHI (34 to 6.5)</td>
<td>43% AHI (47 to 35)</td>
</tr>
<tr>
<td>(Circulation, 2007)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Long-term CPAP adherence in SHF is inadequate (Arzt, Circulation, 2007)

<table>
<thead>
<tr>
<th></th>
<th>CPAP-CSA suppressed n=57</th>
<th>CPAP-CSA unsuppressed n=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (n/hr)</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>P (cm H$_2$O)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>CPAP use at 3 m (hr)</td>
<td>4.6</td>
<td>4.2</td>
</tr>
<tr>
<td>CPAP use at 12 m (hr)</td>
<td>3.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>
Features of ASV devices

- EP to eliminate obstructive events
- Back up rate to abort any impending apnea
- Variable inspiratory support with
  - ↑ hypopneas
  - ↓ hyperpneas
Bi-level

Fixed inspiratory pressure

Fixed inspiratory support = IPAP - EPAP

Fixed expiratory pressure
General operation of ASV devices

- **Hypopnea**: Inspiratory support decreasing during hypopnea
- **Hyperpnea**: Inspiratory support increasing during hyperpnea
- **Expiratory pressure support**: Decreasing during hyperpnea and increasing during hypopnea

**Patients Airflow**

**Device Inspiratory pressure support Expiratory pressure**
A patient with CHF, HCSB on ASV
Effect of ASV on AHI compared to the control in heart failure patients
Modified from Sharma et al, Chest, 2012

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parallel Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASV</td>
<td>38</td>
<td>7</td>
</tr>
<tr>
<td>Control</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>Crossover Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASV</td>
<td>51</td>
<td>6</td>
</tr>
<tr>
<td>Control</td>
<td>50</td>
<td>21</td>
</tr>
</tbody>
</table>

Weighted mean difference in AHI (events/hour)

- Favors ASV
- Favors Control

Weight: Effect size (95% CI)

100%; -14.64 (-21.03, -8.25)
Effects of PAP treatment on survival in patients with SHF and severe sleep apnea (Jilek et al. EJHF, 2011)

N=91, 85% on β blocker
PAP treated; AHI=49/h
16 events, 18%

N=85, 91% on β blocker
untreated; AHI=42
44 events, 52%

Adjusted HR 0.3 (95%CI: 0.2 – 0.6, p=0.001)
Effects of ASV treatment on survival in patients with SHF and severe sleep apnea

Takama and Kurabayashi, Circulation J, 2012
RCT: ASV improves survival in HFpEF and CSA
PSG findings at baseline and 6 months

<table>
<thead>
<tr>
<th>Variable (median)</th>
<th>ASV</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, n/h</td>
<td>37 (7)*</td>
<td>36 (28)</td>
</tr>
<tr>
<td>CAI, n/h</td>
<td>12 (0.1)*</td>
<td>8 (3)</td>
</tr>
<tr>
<td>OAI, n/h</td>
<td>2 (0.3)*</td>
<td>5 (2)</td>
</tr>
<tr>
<td>HI, n/h</td>
<td>16 (3) *</td>
<td>12 (14)</td>
</tr>
<tr>
<td>ArI, n/h</td>
<td>21 (14)*</td>
<td>22 (16)</td>
</tr>
<tr>
<td>Min SaO₂ (%)</td>
<td>78 (90)*</td>
<td>78 (84)</td>
</tr>
</tbody>
</table>

Values in parenthesis are at 6 m.

Yoshihisa et al, Eur J heart Fail, 2012
KM analysis for cardiac events (cardiac death and worsening HF) patients in the ASV and non-ASV groups

In Cox analysis, only use of ASV was an independent predictor of end point:
HR = 0.58, CI = 0.18,0.8, p=0.016
Patients with sleep apnea die in sleep

Gami et al, NEJM, 2006
If I can choose……

Dr, are you telling me that if I use my CPAP I will die during daytime while awake!

I know you mean good, but I prefer to die during sleep
My approach to treat sleep apnea in HF

OSA: CPAP titration (AutoCPAP)( Com SA)
CSA: CPAP titration (AHI< 15/h)
CSA: ASV (CPAP AHI > 15/h)
CSA: Oxygen ( ASV AHI > 15/h)

Key to success: FU, adherence; consider reasons for nonadherence