Apnea-Hypopnea-Index – The “new” old biomarker for Sleep-Disordered Breathing

- Alan S Maisel MD
Importance of Learning about Sleep Apnea

• Sleep apnea is a serious health problem impacting about 20% of US adults\(^1\)

• 75% of severe sleep apnea patients are undiagnosed\(^2\)

• Clinical studies show treating sleep apnea can:\(^3-6\)
  ✓ reduce blood pressure
  ✓ improve left ventricular ejection fraction
  ✓ improve insulin sensitivity
PREVALENCE
Estimated Obstructive Sleep Apnea (OSA) US Population

- Total US Population: 307M
- OSA Population: 52M
- Non-OSA Population: 255M
- Severe OSA: 12M
- Moderate OSA: 11M
- Mild OSA (AHI 5-15): 29M
- Addressable OSA Population: 23M
- Diagnosed: 18.9M
- Undiagnosed: 4.1M
- Treatment of Diagnosed: 3.3M
  - CPAP: 3.1M
  - Surgery: 0.4M
  - Device: Rx/OTC: 0.2M
  - Untreated: 0.2M

Source: McKinsey & Company analysis; Harvard Medical School, 2010
OSA Prevalence in Cardiovascular Disease

Drug Resistant Hypertension\(^1\) - 83%
Congestive Heart Failure\(^2\) - 76%
Pacemakers\(^3\) - 59%
Atrial fibrillation\(^4\) - 49%
All hypertension\(^5\) - 37%
Coronary artery disease\(^6\) - 30%
Angina\(^7\) - 31%

* Male Subjects Only

1 Logan AL et al. J Hypertens 2001
3 Garrigue S et al. Circulation 2007
4 Gami AS et al. Circulation 2004
5 Sjostrom C et al. Thorax 2002
6 Schafer H et al. Cardiology 1999
7 Sanner BM et al. Clin Cardiol 2001
Common Sleep Apnea Risk Factors

- Obesity
- Increasing age
- Endocrine and metabolic
- Male gender
- Anatomic abnormalities of the upper airway
- Smoking
- Cardiovascular
- Alcohol or sedative use
- Family history of sleep problems
- Physical inactivity
- Family history of sleep problems
Types of SDB: OSA

- **Obstructive sleep apnoea (OSA):**
  - Most common type of SDB
  - Caused by recurrent collapse of the upper airway
  - Causes intermittent hypoxia, negative intrathoracic pressure swings, sympathetic activation, systemic inflammation, oxidative stress

Types of SDB: CSA

- **Central sleep apnoea (CSA):**
  - Dysregulation of respiratory control (lack of drive to breathe during sleep)
  - Repetitive periods of reduced ventilation
  - May manifest at CSR (central apnoeas alternating with periods of crescendo-decrescendo respiratory tidal volume)

- Causes increases sympathetic nervous system activity, greater cardiac electrical instability, low frequency oscillations in heart rate and blood pressure

Sleep Apnea – The Basics

- **Apnea Hypopnea Index (AHI)**
  - Number of apneas and hypopneas per hour
  - Apnea = cessation of flow for at least 10 sec
  - Hypopnea = 30% reduction of flow for at least 10 sec with a 4% O₂ desaturation
  - AHI < 5 (normal), AHI 5-14 (mild), AHI ≥ 15 (moderate/severe)

- **Oxygen Desaturation Index (ODI)**
  - Number of O₂ desaturations per hour
  - Based on 4% drop in baseline
Breathing is regulated by:

- Chemoreceptors that monitor blood gas levels $CO_2$ (primarily) and $O_2$ (secondarily)
- The respiratory control center in the brain
Mechanism of OSA

What happens in OSA patients:

- Airway is obstructed
- The level of CO₂ rises (O₂ level falls), signaling patient to breathe
Obstructive Sleep Apnea (OSA) Indicators

- Habitual loud snoring
- Witnessed apneas
- Hypertension
- Excessive daytime sleepiness
- Obesity/neck circumference
- Morning headaches
- Heart failure/CVD
Mechanism of CSA

What happens in CSA patients:

- Airway is open
- Because the level of $CO_2$ is below the patient’s apneic threshold, no signal is sent to breathe
Crossing the Threshold

What is the apneic threshold?

When a patient’s CO$_2$ level falls below normal range and enters the apneic threshold, a central apnea occurs.
Pathophysiological Effects of OSA

**Arousal:**
- ↑ HR & ↑ BP
- ↑ Minute ventilation
- Neurohormonal imbalance
- Sleep fragmentation

**Sleep Fragmentation—sleep debt:**
- Neurohormonal imbalances
- Behavioral changes

**Intrathoracic pressure changes:**
- Overdistends R atrium and ventricle
- Shifts intraventricular septum to left
- ↑ Afterload
- ↓ Cardiac output

**Desaturation (hypoxemia):**
- ↑ Sympathetic response
- ↑HR & ↑BP
- Arrhythmias
- ↑ coagulability and clot formation
- Deoxygenation-reoxygenation causes endothelial dysfunction
Cardiovascular Disease Development

**OSA**
- Hypoxemia
- Reoxygenation
- Hypercapnia
- Intrathoracic pressure
- Arousals
- Sleep deprivation

**Disease Mechanisms**
- Sympathetic activation
- Metabolic dysregulation
- Left atrial enlargement
- Endothelial dysfunction
- Hypercoagulability

**Associated CV Disease**
- Hypertension
- Heart failure
- Arrhythmias
- Renal disease
- Stroke
- Myocardial infarction

Sudden Cardiac Death

SDB in Heart Failure

- Prevalence rates of 50-75\(^1\)
  - More common than in the general population
- With preserved (HFpEF) or reduced (HFrEF) ejection fraction
- Relative lack of typical symptoms (especially daytime sleepiness)\(^7\)
- Lack of recognition and diagnosis
OUTCOMES
Sleep Apnea Testing and Outcomes in a Large Cohort of Medicare Beneficiaries with Newly Diagnosed Heart Failure

Shahrokh Javaheri¹, E. Ben Caref², Er Chen³, Kuo Bianchini Tong³, and William T. Abraham⁴

¹Sleepcare Diagnostics, Cincinnati, Ohio; ²Medtelligence, LLC, Philadelphia, PA; ³Quorum Consulting Inc., San Francisco, California; and ⁴Division of Cardiovascular Medicine, The Ohio State University Heart Center, Columbus, Ohio

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**Percent of Cohort Alive**

- Tested, Diagnosed, Treated, N=258
- Not Tested, Not Treated, N=30,065

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

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**Figure 2.** Kaplan-Meier survival curves for the tested, diagnosed, and treated subjects versus not tested and not treated subjects, adjusted by age, sex, and Charlson Comorbidity Index, 2004 through 2005. CI = confidence interval; HF = heart failure.
Survival – SDB in HF

Cut off AHI ≥ 15/h

Bitter et al., Eur Heart J 2010
CSA and Mortality in HF

Jilek et al., EJHF 2011
CSA Predictor Cardiac Readmission

Khayat et al., J Cardiac Fail 2012
TREATMENT
PAP Therapy

- **CPAP**
  - Constant Positive Airway Pressure

- **Automatic Positive Airway Pressure (APAP)**
  - Variable pressure levels

- **Bilevel**
  - Two-level pressure system
Cardiovascular Effects of Continuous Positive Airway Pressure in Patients with Heart Failure and Obstructive Sleep Apnea

[Original Articles]

Kaneko, Yasuyuki; Floras, John S.; Usui, Kengo; Plante, Julie; Tkacova, Ruzena; Kubo, Toshihiko; Ando, Shin-ichi; Bradley, T. Douglas.

From the Sleep Research Laboratories, Toronto Rehabilitation Institute (Y.K., K.U., J.P., R.T., T.D.B.); Toronto General Hospital-University Health Network and Mount Sinai Hospital (J.S.F., T.K., S.A., T.D.B.); and the Department of Medicine and the Centre for Sleep Medicine and Circadian Biology, University of Toronto (Y.K., J.S.F., K.U., J.P., R.T., T.D.B.) - all in Toronto. Address reprint requests to Dr. Bradley at the Toronto General Hospital/UHN, NU 9-112, 200 Elizabeth St., Toronto, ON M5G 2C4, Canada, or at douglas Bradley@utoronto.ca.
What is ASV?

- Adaptive servo-ventilation (ASV) is a non-invasive ventilatory therapy that supports inspiration when breathing amplitude is reduced and ensures sufficient respiration when respiratory effort is absent (variable IPAP).
- Upper airway patency is ensured by provision of end-expiratory pressure (fixed or variable EPAP).

**ASV vs Other PAP**

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>AIM</th>
<th>FEATURES</th>
<th>PRESSURE PROFILE</th>
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<tbody>
<tr>
<td>CPAP</td>
<td>Maintain upper airways open</td>
<td>Fixed or automatically adjusted expiratory pressure</td>
<td><img src="image" alt="CPAP Pressure Profile" /></td>
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<tr>
<td>APAP</td>
<td>Maintain upper airways open</td>
<td>Continually adjusting expiratory pressure to optimal level for specific patient needs</td>
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<tr>
<td>BPAP</td>
<td>Support breathing in lung disease-related respiratory insufficiency</td>
<td>Fixed expiratory pressure and pressure support at inspiration, usually with fixed backup rate</td>
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<tr>
<td>ASV</td>
<td>Maintain upper airways open</td>
<td>Continually adjusting expiratory pressure to optimal level according to specific patient needs</td>
<td><img src="image" alt="ASV Pressure Profile" /></td>
</tr>
</tbody>
</table>

APAP, auto-adjusting positive airway pressure; ASV, adaptive servoventilation; BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

ASV and Minute Ventilation

ASV responds to changes in minute ventilation

Monitors recent average minute ventilation (~3-min window)
It continuously calculates a target ventilation throughout the night (90% of recent average ventilation)
Adjusts pressure support up or down as needed to achieve target
Bilevel device in CPAP Mode

CSR Pattern

SpO₂ variable 90-98%

Pulse rate variable 77-91 beats per min
Switch from CPAP to ASV mode

Respiratory pattern beginning to normalize

SpO₂ stabilizing

Less variability in pulse rate
Respiratory pattern completely normalized

SpO$_2$ stable 94-97%

Pulse rate stable 73-77 beats per min
Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure

Martin R. Cowie, M.D., Holger Woehrle, M.D., Karl Wegscheider, Ph.D., Christiane Angermann, M.D., Marie-Pia d’Ortho, M.D., Ph.D., Erland Erdmann, M.D., Patrick Levy, M.D., Ph.D., Anita K. Simonds, M.D., Virend K. Somers, M.D., Ph.D., Faiez Zannad, M.D., Ph.D., and Helmut Teschler, M.D.

ABSTRACT

BACKGROUND
Central sleep apnea is associated with poor prognosis and death in patients with heart failure. Adaptive servo-ventilation is a therapy that uses a noninvasive ventili-
SERVE HF: Objective

To investigate the effects of adding ASV to guideline-based medical management on survival and cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFrEF) and predominant CSA\textsuperscript{1,2}

SERVE-HF: Endpoints

- Primary composite endpoint:
  - Time first event of all-cause death, life-saving cardiovascular intervention*, or unplanned hospitalization for worsening chronic HF

- Secondary endpoints:
  - As for primary endpoint, but cardiovascular vs all-cause death
  - As for primary endpoint, but all-cause vs HF-related unplanned hospitalization
  - Time to death (all-cause)
  - Time to cardiovascular death
  - Change in NYHA class
  - Change in 6MWD
  - Quality of life

*heart transplant, long-term ventricular assist device, resuscitation of sudden cardiac arrest, or appropriate ICD shock
Primary Endpoint Neutral

Time to first event of all-cause death, life-saving cardiovascular intervention, or unplanned hospitalization for worsening chronic HF

Cumulative incidence rate (%)

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HR 1.13, 95% CI 0.97, 1.31; P = 0.10

Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].
### Subgroup Analysis: 1° Endpoint

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients total n</th>
<th>ASV incidence per p-year</th>
<th>Control better</th>
<th>p-value for interaction</th>
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All-Cause Death

HR 1.28, 95% CI 1.06, 1.55; P = 0.01

Cumulative incidence rate (%)

No. at Risk

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Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].
Cardiovascular Death

HR 1.34, 95% CI 1.09,1.65; P=0.006

No. at Risk

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### Subgroup Analysis: CV Death

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<th>Patients total n</th>
<th>ASV incidence</th>
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<tr>
<td>≥ 28</td>
<td>680</td>
<td>0.078</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>326</td>
<td>0.196</td>
<td>0.105</td>
<td>0.01</td>
</tr>
<tr>
<td>≥ 30</td>
<td>743</td>
<td>0.069</td>
<td>0.066</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- Addition of ASV to guideline-based medical management does not improve outcomes in patients with HFrEF and CSA despite effective control of CSA.
- These results apply only to the population studied.
  - Cannot be generalised to patients with HF with preserved ejection fraction, or those with predominant OSA.

Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].
### Sleep Disorders

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>C-LD</td>
<td>In patients with NYHA class II–IV HF and suspicion of sleep disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable.</td>
<td>NEW: Recommendation reflects clinical necessity to distinguish obstructive versus central sleep apnea.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>Sleepiness, abnormal sleep architecture, cardiovascular disease and excessive daytime sleepiness, an assessment is reasonable. CPAP may be reasonable to improve sleep quality and daytime sleepiness.</td>
<td>NEW: Limited data demonstrates the limited scope of benefit expected from CPAP for obstructive sleep apnea.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>In patients with NYHA class II–IV HF/EF and central sleep apnea, adaptive servo-ventilation causes harm.</td>
<td>NEW: New data demonstrate a signal of harm when adaptive servo-ventilation is used for central sleep apnea.</td>
</tr>
</tbody>
</table>
LIFE IS NOT THE WAY IT’S SUPPOSED TO BE... IT’S THE WAY IT IS... THE WAY WE COPE WITH IT, IS WHAT MAKES THE DIFFERENCE.