HEART FAILURE IN CENTRAL SLEEP APNEA

PETER C. GAY, MD, MSc

PROFESSOR OF MEDICINE
MAYO CLINIC
ROCHESTER, MN

PETER C. GAY, MD, is Professor of Medicine, Mayo Medical School, Rochester, MN where he has been on staff since 1988. He also is Consultant, Division of Pulmonary, Critical Care and Sleep Medicine.

In 1976 he graduated with a B.A. from Middlebury College, Middlebury, VT. In 1981, he earned an MS in Physiology and his MD at the University of Hawaii, Honolulu, HI. He received all of his graduate training at Mayo Clinic Rochester and is Board Certified in Internal Medicine, Subspeciality Pulmonary Disease, Critical Care Medicine, and Sleep Medicine.

He is the recipient of multiple national education and leadership awards including the NAMDRC’s President’s Award for his work in developing national coverage criteria for non-invasive positive pressure ventilation and the 2015 invited lecturer honoring Professor Walter J. O’Donohue. Dr. Gay is a former President and multi-term board member of NAMDRC and the Society of Anesthesia and Sleep Medicine. He is past chair of the ACCP Home Care Network and has directed and participated in many sleep board review courses, edited and authored many books, chapters, and position papers in the field of sleep medicine. He has contributed to several pivotal multi-center trials for patients with complex sleep-related breathing disorders and guided the development for the current CMS central apnea reimbursement criteria.

OBJECTIVES:
1. Justify upfront topic value
2. Note Central Apnea Definitions
3. Offer mechanisms for CSA
4. Note prevalence and Risks
5. Provide diagnostic plan
6. Review past and newest therapies
NAMDRC 42nd Annual Meeting
Advances in Pulmonary, Critical Care and Sleep Medicine
Sonoma, California
Thursday 9:30 AM
March 14, 2019

Heart Failure in Central Sleep Apnea

Peter C Gay MD
Professor of Medicine
Mayo Clinic Rochester, MN

No conflicts to declare
Outline

• Objectives
• Background
  • Definitions
  • Mechanisms
  • Prevalence
• Recognition and Diagnosis
• Treatment
  • Past, present, future treatment

Objectives

• Justify upfront topic value
• Note Central Apnea Definitions
• Offer mechanisms for CSA
• Note prevalence and Risks
• Provide diagnostic plan
• Review past and newest therapies
ICSD-2
Central Sleep Apnea Syndromes

(1) Primary Central Sleep Apnea
(2) Central Sleep Apnea Due to Cheyne Stokes Breathing Pattern
(3) Central Sleep Apnea Due to Medical Condition Not Cheyne Stokes
(4) Central Sleep Apnea Due to High-Altitude Periodic Breathing
(5) Central Sleep Apnea Due to Drug or Substance
(6) Primary Sleep Apnea of Infancy

Complex Sleep Apnea
AASM Viewpoint

• Complex Sleep Apnea Syndrome is characterized by the emergence or persistence of central respiratory events during CPAP or BPAP titration for treatment of OSA.
• The available evidence was considered insufficient to warrant a treatment recommendation.
CSR/CSA Defined

• Breathing pattern of progressively deeper, and sometimes faster, breathing followed by a gradual decrease that results in a repetitive pattern

• Usual periodicity of 70-90 seconds with a crescendo-decrescendo pattern oscillating between apnea and hyperpnea associated with changing in gas exchange

• Hunter-Cheyne-Stokes respiration (CSR)/central sleep apnea (CSA) common in CHF pts and associated with increase in mortality in patients with CHF

Prognostic Value of Nocturnal Cheyne-Stokes Respiration in Chronic Heart Failure

• **Methods:**
  • Sixty-two CHF patients with left ventricular ejection fraction <35%, NYHA class II to III
  • Clinical evaluation, Echo, spirometry, phenylephrine test, Holter recording
  • PSG to evaluate the occurrence of CSR, and apnea/hypopnea index (AHI)
  • Mean follow-up of 28+13 months
AHI is a powerful independent predictor of poor prognosis in clinically stable patients with CHF. The presence of an AHI >30/h adds prognostic information compared with other clinical, Echo, and autonomic data. Identifies pts at very high risk for subsequent cardiac death.

### TABLE 1. Baseline Characteristics According to Mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>Survivors</th>
<th>Non-survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs.</td>
<td>57±19</td>
<td>56±19</td>
<td>58±10</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>8.5 (5.0)</td>
<td>8.0 (5.0)</td>
<td>9.4 (6.8)</td>
</tr>
<tr>
<td>Peak VO₂, rel - kg⁻¹·min⁻¹</td>
<td>15.9±5.6</td>
<td>16.7±4.5</td>
<td>12.0±3.4</td>
</tr>
</tbody>
</table>

**Medications**
- Digoxin: 49 (76) 27 (95) 14 (89)
- ACE inhibitors: 46 (85) 34 (87) 12 (85)
- Diuretics: 48 (89) 34 (87) 14 (85)
- Nitrates: 28 (52) 17 (31) 11 (73)
- Antiarrhythmics: 11 (20) 6 (15) 5 (30)

**Echocardiographic data**
- LVET, %: 23±6 24±1.7 21±4
- LVEDV, ml/m²: 107±43 127±54 185±25
- LVEF, ml/m²: 109±59 96±42 112±22
- Early Dec time, ms: 150±68 150±51 127±34
- LA area, cm²: 25±7 25±6 28±6
- RA area, cm²: 17±6 16±5 20±6
- PCWP, mm: 30±8 30±7 45±7
- MR moderate-severe: 96 (17) 23 (59) 13 (67)
- TR moderate-severe: 12 (22) 7 (17) 5 (30)

**Sleep data**
- AHI, n/h: 25±20 26±15 36±7

### TABLE 2. Mortality Odds According to AHI and LA Area

<table>
<thead>
<tr>
<th>AHI, n/h</th>
<th>LA Area, cm²</th>
<th>LA Area, 15 cm²</th>
<th>Area 30, cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.17</td>
<td>0.43</td>
<td>0.68</td>
</tr>
<tr>
<td>20</td>
<td>0.31</td>
<td>0.77</td>
<td>1.22</td>
</tr>
<tr>
<td>30</td>
<td>0.65</td>
<td>1.39</td>
<td>2.19</td>
</tr>
<tr>
<td>35</td>
<td>0.74</td>
<td>1.86</td>
<td>2.54</td>
</tr>
<tr>
<td>40</td>
<td>0.90</td>
<td>2.49</td>
<td>3.04</td>
</tr>
</tbody>
</table>

**Recognition and management of complex sleep-disordered breathing**


Complex sleep-disordered breathing is a distinct form of sleep apnea. It has recognizable characteristics that are present without, and often worsened during, positive airway pressure treatment.
Complex Sleep Apnea Response (CompSA)

Baseline Diagnostic PSG - Severe OSA

CPAP = 10 cmH2O
### Complex Sleep Apnea Response (CompSA)

- LOC
- ROC
- Fpz-Cz
- Cz-Oz
- C4-A1
- Chin
- Leg
- ECG
- VEST
- Sono
- SaO2
- SUM
- RC
- ABD
- ASV P
- O2/HR

**ASV Default Mode with EEP= 7 cmH2O**

### Treatment Emergent Centrals

A graph showing various electrical activities with annotations and markers indicating different phases or events.
Pts with CSA/CSR do not always respond to CPAP or oxygen
NPPV and ASV have previously been shown to improve sleep disordered breathing (SDB) in CSA/CSR or CompSA pts
We hypothesized that NPPV and ASV would be equivalent but superior to CPAP judged by improvements in apnea/hypopnea index (AHI) and respiratory arousal index (RAI) as endpoints.
PSG features prior to Study Nights

<table>
<thead>
<tr>
<th>PSG Finding</th>
<th>C-ASCSR N=6</th>
<th>Camp SAS N=6</th>
<th>Mixed N=7</th>
<th>Combined N=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea Hypopnea Index</td>
<td>Diagnostic</td>
<td>CPAP</td>
<td>Diagnostic</td>
<td>CPAP</td>
</tr>
<tr>
<td>Central Apnea Index</td>
<td>22.7±14.9</td>
<td>2.8±10.3</td>
<td>20.8±13.7</td>
<td>2.7±10.6</td>
</tr>
<tr>
<td>Obstructive Apnea Index</td>
<td>4.7±4.8</td>
<td>0.8±1</td>
<td>5.6±8.2</td>
<td>6.6±7.8</td>
</tr>
<tr>
<td>Hypopnea Index</td>
<td>17.8±14.7</td>
<td>12.8±18.6</td>
<td>23.8±28.6</td>
<td>19.8±22.5</td>
</tr>
<tr>
<td>Respiratory Arousal Index</td>
<td>47.4±20.4</td>
<td>24.8±20.9</td>
<td>62.1±20.4</td>
<td>37.3±21.5</td>
</tr>
<tr>
<td>Mean Qsat</td>
<td>94.6±3.7</td>
<td>94.6±3.7</td>
<td>92.6±3.5</td>
<td>94.6±3.7</td>
</tr>
</tbody>
</table>

-21 of 23 pts completed all studies, mean age and body mass index = 65±12.4 (SD) yrs. and 312±4.9 mg/m2.
- Diagnostic AHI= 54.7±23.8, and RAI= 45.6±25.8
- Following attempted optimal titration with CPAP (15 pts), disturbed breathing and sleep remained high with mean AHI= 34.3±25.7 and RAI= 32.1±29.7.
- AHI with either NPPV or ASV respectively (6.2±7.6 or 0.8±2.4) and RAI (6.4±6.2 or 2.4±4.5) improved markedly from baseline.
- AHI and RAI significantly superior using ASV (p<0.02)

PSG features of NPPV vs ASV

<table>
<thead>
<tr>
<th>Polysomnography Finding</th>
<th>NPPV</th>
<th>ASV</th>
<th>Difference (ASV-NPPV)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea Hypopnea Index</td>
<td>6.2±7.6</td>
<td>0.8±2.4</td>
<td>-5.4±7.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Central Apnea Index</td>
<td>0.6±1</td>
<td>0.0±2</td>
<td>-0.6±1</td>
<td>0.019</td>
</tr>
<tr>
<td>Obstructive Apnea Index</td>
<td>0.4±0.9</td>
<td>0.0±2</td>
<td>-0.4±0.7</td>
<td>0.044</td>
</tr>
<tr>
<td>Hypopnea Index</td>
<td>5.3±7.3</td>
<td>0.8±2.2</td>
<td>-4.6±7.1</td>
<td>0.008</td>
</tr>
<tr>
<td>Respiratory Arousal Index</td>
<td>6.4±8.2</td>
<td>2.4±4.5</td>
<td>-4.0±6.7</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean Qsat</td>
<td>91.6±5.5</td>
<td>92.4±5.1</td>
<td>-0.8±3.2</td>
<td>0.577</td>
</tr>
<tr>
<td>Oxygen Desaturation Index</td>
<td>4.4±2.9</td>
<td>2.7±4.4</td>
<td>-1.7±6.1</td>
<td>0.053</td>
</tr>
<tr>
<td>Sleep Architecture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Sleep Time (min)</td>
<td>344.7±59.2</td>
<td>336.8±43.5</td>
<td>-7.8±53.8</td>
<td>0.513</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>79.7±9.2</td>
<td>81±7.6</td>
<td>1.4±9</td>
<td>0.491</td>
</tr>
<tr>
<td>STAGE 1 (%)</td>
<td>13.2±9.7</td>
<td>13.2±10.1</td>
<td>0.1±6</td>
<td>0.952</td>
</tr>
<tr>
<td>STAGE 2 (%)</td>
<td>58.7±15.7</td>
<td>60.7±16</td>
<td>2±12.2</td>
<td>0.461</td>
</tr>
<tr>
<td>SWIS (%)</td>
<td>9.4±9</td>
<td>9.4±9</td>
<td>-0.0±10</td>
<td>0.528</td>
</tr>
<tr>
<td>REM (%)</td>
<td>17.4±8.4</td>
<td>16.5±10</td>
<td>-0.8±7.6</td>
<td>0.614</td>
</tr>
<tr>
<td>Total Arousal Index</td>
<td>23.9±12.5</td>
<td>24.9±13.2</td>
<td>1±10.2</td>
<td>0.650</td>
</tr>
</tbody>
</table>

*CPAP PSG not done. **Combined data on CPAP only for 15/21 pts
Mechanisms
CHF with CSR
• High controller gain > 1:1 (increased CO2 sensitivity)- exaggerated responsiveness
• Hypocapnia resulting from lung edema (high filling pressures)
• Long circ time with slowed trigger time
• Uncommon during REM sleep, likely due to decreased controller gain

Javaheri S. A mechanism of central sleep apnea in patients with heart failure. NEJM 1999; 341: 949-954

Mechanisms
Complex Sleep Apnea
• Mechanisms not well understood
• Dual Causation
  • Anatomic and Physiologic vulnerability to OSA
  • Central breathing control instability leading to chemo-reflux dysfunction similar to CSR but shorter periodicity

Peter C Gay. Complex Sleep Apnea: It Really Is a Disease.
Mechanisms
Complex Sleep Apnea

• Provoked by high CPAP pressures in OSA pts obstructive sleep apnea syndrome

• The enhanced chemoreceptor sensitivity, causes pronounced sleep fragmentation in essence provoking a sleep wake transitional apnea


Complex Sleep Apnea (CompSA)

• Differences in Pts with CompSA:
  • Males- 81% vs 60% men in OSA pts (p < 0.05)
  • CPAP suppressed OSA but the residual AHI, mostly from central apneas, remained high:
    • CompSA= 21.7 ± 18.6 and CSA= 32.9 ± 30.8 in CSA vs in OSAHS= 2.1 ± 3.1 (p< 0.001).

• CONCLUSIONS: CompSA pts are most similar to pts with OSAHS until CPAP is applied. Clinical risk factors do not predict the emergence of CompSA.

Morgenthaler TI, Sleep 29(9) 1203-9 (2006)
**Prevalence**

Prevalence of CSA varies with forms of CSA

- **Situational**
  - Most healthy individuals develop periodic breathing upon high altitude ascent

- **Idiopathic CSA**

- **With CHF - Cheyne Stokes and Complex**
  - Recent prospective prevalence study of CHF pts with left ventricular ejection fraction <45% revealed 37% of pts had CSR type CSA- Javaheri *Int J Cardiol* 2006.

**Persistence - Complex Sleep Apnea (CompSA)**

Role of Drop Out and AHI<5 on CPAP

Morgenthaler et al, CompSAS Resolution trial, Late-breaking abstract 2012
Screening/Diagnosis
CHF and CSR

The Big Five

• NYHA ≥3
• A Fib
• EF~20%
• Mitral Regurgitation
• Male
**Treatment options**

- Treatment of underlying CHF problem
  - Drugs- Pharmacologic Phrenzy
  - Sparks-Atrial Pacing, Cardiac Resynchronization Therapy
- Treatment of Central Apnea- Clinical trials old and new
  - Gas- Oxygen
  - PAP- CPAP, ASV
  - Sparks- Phrenic nerve pacing

**Oxygen for OSA**

- Mainstay in 1990s
  
  *Javaheri S et al. Effects of nasal O2 on sleep related disordered breathing in stable CHF. Sleep 1999;22:1101-6*

- AASM Practice Parameter Guideline in 2012-
  Nocturnal O2 is indicated for the treatment of CSAS related to CHF. (STANDARD)
  
  *Potential mechanisms include hyperoxia induced reduced CO2 sensitivity with lower controller gain
  *Improved AHI (hypopnea artifact?) and cardiac LVEF.
  *The duration of therapy with oxygen varied from a single night to 12 months but supportive

  *Equivocal data and lack of reimbursement urged further research so Javaheri just launched funded randomized NIH trial with O2*

**Effects of CPAP on CV Outcomes in CHF Pts With and Without CSR**

**Methods**
- Randomized, controlled trial- 66 CHF pts with CHF (29 with and 37 without CSR-CSA) randomized to CPAP or not

**Results**
- Stratified analysis revealed CSR-CSA pts using CPAP had a significant (8%) improvement in LVEF at 3 mos. and a relative risk reduction of 81% in mortality or cardiac TX

**Conclusions- With CPAP:**
- Improved cardiac function only in CHF pts with CSR-CSA
- May reduce the combined mortality–cardiac TX rate in those CHF patients with CSR-CSA who comply with CPAP.

*Sin D, Bradley TD. Circ 2000. 102(1): 61-66*

**Use CPAP or Die**
Methods:

After medical therapy was optimized, 258 CHF pts (EF=24.5±8%) with CSA (AHI= 40±16/hr) were randomly assigned to CPAP or not for mean 2 yrs.

CPAP for CSA and CHF
Bradley TD, CANPAP Investigators. NEJM 353(19), 2005

### Table 1: Baseline Characteristics of the Patients. *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (N=120)</th>
<th>CPAP Group (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.5±9.8</td>
<td>63.2±9.3</td>
</tr>
<tr>
<td>Male sex (%</td>
<td>123 (65)</td>
<td>125 (68)</td>
</tr>
<tr>
<td>White race (%)</td>
<td>123 (65)</td>
<td>125 (68)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.3±6.3</td>
<td>28.8±5.3</td>
</tr>
<tr>
<td>NYHA class — no. (%)</td>
<td>II (66)</td>
<td>II (67)</td>
</tr>
<tr>
<td>Ischemia (%)</td>
<td>68 (68)</td>
<td>63 (65)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>40 (33)</td>
<td>30 (23)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction — %</td>
<td>24.4±7.6</td>
<td>24.8±7.7</td>
</tr>
</tbody>
</table>

Medication — no. (%)
- ACE inhibitors: 106 (88) vs. 99 (77)
- AII blockers: 23 (19) vs. 24 (19)
- Beta-blockers: 99 (83) vs. 98 (77)
- Loop diuretics: 210 (87) vs. 210 (86)
- Spironolactone: 46 (39) vs. 43 (34)
- Digoxin: 74 (62) vs. 60 (52)
- Nitroglycerin: 38 (32) vs. 31 (24)

Sleep time — min
- Total sleep: 308±84 vs. 308±82
- Stage 1 sleep: 58±18 vs. 58±18
- Stage 2 sleep: 17±75 vs. 17±65
- Stage 3 and 4 sleep: 3±68 vs. 3±62
- REM sleep: 40±25 vs. 41±27

Central apnea and hypopnea — %
- Mean SaO2 during sleep — %
- Lows: 81.7±6.5 vs. 82.1±8.3

Effect of CPAP on AHI, Mean/Min SpO2, and LV Ejection Fraction

### CPAP Resulted in Sig Long-term Reductions:
- **AHI (Panel A)**

**Increased:**
- **Mean SpO2 (Panel B)**
- **LVEF (Panel C)**
- **Min SpO2 (Panel D)**
CPAP for CSA and CHF
Bradley TD, CANPAP Investigators. NEJM 353(19), 2005

Death or Heart Transplant per 100 Person-Years for the 2 groups combined fell from 83 to 17% of the predicted rate during the trial.

• No difference in transplant-free survival rate for control and CPAP groups (P=0.54).

CPAP for CSA and CHF
Bradley TD, CANPAP Investigators. NEJM 353(19):2025-33, 2005

Early shift favored controls (P=0.02) but changed after 18 months favoring CPAP (P=0.06).
**CPAP for CSA and CHF**
Bradley TD, CANPAP Investigators. NEJM 353(19), 2005

**Conclusions:**

- CPAP attenuated central sleep apnea, improved nocturnal oxygenation, increased the ejection fraction, lowered Norepinephrine levels, and increased the 6 min walk distance.
- It did not affect survival so data do not support use of CPAP to extend life in pts with central sleep apnea and CHF.

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**Adaptive Servo-Ventilation (ASV): Novel Treatment for Cheyne-Stokes Respiration in Heart Failure**

**A** Typical 5-min polygraph recording on the diagnostic night with desaturations and arousals.

**(B)** Typical 5-min polygraph recording on the adaptive servo-ventilation night.
Adaptive Servo-Ventilation (ASV): Novel Treatment for Cheyne-Stokes Respiration in Heart Failure


Central apnea arousals most reduced for ASV but Total arousal reduction same for Bi-Level and ASV

Compliance and efficacy of ASV vs CPAP for Cheyne-Stokes respiration in heart failure over a 6 mos period Carole Philippe Heart 20 Jun 2005

Methods:

• 25 pts (age: 28-80y, NYHA: II-IV) with stable CHF and CSA-CSR were randomized to either CPAP or ASV

• Groups were comparable for NYHA class, LVEF, medical treatment, BMI and CSA-CSR.
Compliance and efficacy of ASV vs CPAP for Cheyne-Stokes respiration in heart failure over a 6 mos period
Carole Philippe Heart 20 Jun 2005

AHI in both groups at baseline and after 3 and 6 mos of treatment with either ASV or CPAP

Panel B shows the difference between baseline AHI and AHI measured at 3 and 6 months.

ASV induced a greater decrease in AHI than CPAP.

Clinical Trial – SERVE-HF
MR Cowie et al. NEJM 2015;122:659-66

METHODS
We randomly assigned 1325 patients with a left ventricular ejection fraction of 45% or less, an apnea-hypopnea index (AHI) of 15 or more events (occurrences of apnea or hypopnea) per hour, and a predominance of central events to receive guideline-based medical treatment with adaptive servo-ventilation or guideline-based medical treatment alone (control). The primary end point in the time-to-event analysis was the first event of death from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock), or unplanned hospitalization for worsening heart failure.
Table 2. Respiratory Characteristics at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (N=659)</th>
<th>Adaptive Servo-Ventilation (N=666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epworth Sleepiness Scale score†</td>
<td>7.1±4.6</td>
<td>7.0±4.3</td>
</tr>
<tr>
<td>AHI — no. of events/hr</td>
<td>31.7±13.2</td>
<td>31.2±12.7</td>
</tr>
<tr>
<td>Central apnea index/total AHI — %</td>
<td>46.5±30.0</td>
<td>44.6±28.9</td>
</tr>
<tr>
<td>Central AHI/total AHI — %</td>
<td>81.8±15.7</td>
<td>80.8±15.5</td>
</tr>
<tr>
<td>Oxygen desaturation index — no. of events/hr‡</td>
<td>32.8±19.0</td>
<td>32.1±17.7</td>
</tr>
<tr>
<td>Oxygen saturation — %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>92.8±2.5</td>
<td>92.8±2.3</td>
</tr>
<tr>
<td>Minimum</td>
<td>80.3±7.5</td>
<td>80.7±7.0</td>
</tr>
<tr>
<td>Time with oxygen saturation &lt;90% — min</td>
<td>55.7±73.9</td>
<td>50.5±68.2</td>
</tr>
</tbody>
</table>

CV Deaths

C Death from Cardiovascular Causes

Hazard ratio, 1.34 (95% CI, 1.09–1.65)
P=0.006

No. at Risk
Control 659 563 491 334 213 117
ASV 666 533 466 304 189 97
Incidence of Endpoint Events

### Table 3. Incidence of Endpoint Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Control (N=639)</th>
<th>Adaptive Soro-Ventilation (N=666)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients (%)</td>
<td>No. of Events/Yr (95% CI)</td>
<td>No. of Patients (%)</td>
<td>No. of Events/Yr (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint†</td>
<td>335 (50.8)</td>
<td>0.212 (0.190-0.236)</td>
<td>360 (54.1)</td>
<td>0.285 (0.220-0.372)</td>
</tr>
<tr>
<td>First secondary endpoint†</td>
<td>317 (48.1)</td>
<td>0.200 (0.179-0.224)</td>
<td>345 (51.8)</td>
<td>0.235 (0.211-0.261)</td>
</tr>
<tr>
<td>Second secondary endpoint†</td>
<td>445 (70.6)</td>
<td>0.405 (0.365-0.444)</td>
<td>482 (72.4)</td>
<td>0.441 (0.403-0.483)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>193 (29.3)</td>
<td>0.094 (0.081-0.107)</td>
<td>232 (34.8)</td>
<td>0.119 (0.104-0.135)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>578 (97.0)</td>
<td>0.076 (0.065-0.088)</td>
<td>679 (99.9)</td>
<td>0.102 (0.088-0.117)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>448 (68.0)</td>
<td>0.384 (0.349-0.421)</td>
<td>529 (79.9)</td>
<td>0.411 (0.388-0.433)</td>
</tr>
<tr>
<td>Unplanned hospitalization for worsening heart failure</td>
<td>272 (41.3)</td>
<td>0.164 (0.145-0.185)</td>
<td>287 (43.1)</td>
<td>0.190 (0.169-0.214)</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>12 (1.8)</td>
<td>0.006 (0.003-0.010)</td>
<td>8 (1.2)</td>
<td>0.004 (0.002-0.008)</td>
</tr>
<tr>
<td>Implantation of long-term VAD</td>
<td>10 (1.5)</td>
<td>0.005 (0.002-0.009)</td>
<td>16 (2.4)</td>
<td>0.008 (0.005-0.013)</td>
</tr>
<tr>
<td>Resuscitation</td>
<td>19 (2.9)</td>
<td>0.009 (0.006-0.014)</td>
<td>25 (3.8)</td>
<td>0.013 (0.008-0.019)</td>
</tr>
<tr>
<td>Resuscitation for cardiac arrest</td>
<td>16 (2.4)</td>
<td>0.008 (0.004-0.013)</td>
<td>18 (2.7)</td>
<td>0.009 (0.005-0.015)</td>
</tr>
<tr>
<td>Appropriate shock</td>
<td>65 (9.9)</td>
<td>0.013 (0.006-0.024)</td>
<td>45 (6.8)</td>
<td>0.026 (0.017-0.032)</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>35 (5.3)</td>
<td>0.017 (0.012-0.024)</td>
<td>31 (5.0)</td>
<td>0.017 (0.012-0.024)</td>
</tr>
</tbody>
</table>

Possible Explanations

A. Imbalances in randomization creating introduction of confounding conditions and conclusions are dubious
B. Disfavorable hemodynamic effects of positive pressure,
C. Potential protective benefits of CSA perhaps through autonomic or conduction system mechanisms
D. Pro-arrhythmic effects through metabolic or electrolyte abnormalities.
E. All of the above are plausible

But what about the devices??
Comparison of Physiological Performance of Four Adaptive Servo Ventilation Devices In Pts With Complex Sleep Apnea
Sai Parthasarathy et al

- ASV treatment of sleep disordered breathing in patients with heart failure with predominant central sleep apnea increased risk for mortality (SERVEHF) and device algorithms controlling respiratory rate and pressure support may have led to adverse events
- METHODS: Cross-over of patients with complex sleep apnea with preserved cardiac contractility EF > 45% who were adherent to ASV randomly assigned to 4 nts of PSG on the device used in SERVE-HF trial (S7 VPAP Adapt); a later version device (S9 VPAP Adapt); Philips ASV (System One); and a later version Philips ASV (Dreamstation).
- EPAP level set from 4 to 15 cm H2O; minimum pressure support (PSmin) at lowest level (3 cm H2O for S7 device and 0 cm H2O for all others); Pmax was 15 cm H2O with max total of 25 cm H2O with automatic back-up rate with the same mask interface on all nights.

Comparison of Physiological Performance of Four Adaptive Servo Ventilation Devices In Patients With Complex Sleep Apnea
Sai Parthasarathy et al

- 14 pts underwent PSG on 4 nts from 4 different devices. Ve was greater during S7 device than all other devices during wakefulness (P<0.0001) and for the entire night (P<0.02). The Respiratory rate was also greater during S7 device when compared to the S9 device for the entire night (P<0.0001).
- During wakefulness, PS level was greater during S7 device therapy when compared to S9 device (P=0.002; table) and tended to be greater than PS level administered by S9 device during sleep (P=0.085)
- Significant differences in Ve and sleep architecture while receiving ASV therapy from various devices resulted in higher Ve and adverse effects of ASV may be secondary to high minute ventilation (Ve) that caused hypocapnia and consequent arrhythmia
Comparison of Physiological Performance of Four Adaptive Servo Ventilation Devices In Patients With Complex Sleep Apnea
Sai Parthasarathy et al

- Privacy laws in Europe have changed significantly recently which makes it even harder to get data out of Europe. This is being retrofitted to existing data as well and so we may have the issue of not having the exact permissions to extract data and send to the US. Even though it is de-identified it doesn’t solve all the privacy issues
- Our requests to obtain the SERVE-HF European data and US data are essentially denied

Next Steps
Transvenous Phrenic Nerve Stim

- TPNS neurostimulator is placed in the right pectoral area, and a stimulation lead is placed via a subclavicular approach into the left pericardiophrenic vein with a second sensing lead placed in the azygos vein. The neurostimulator stimulates the phrenic nerve, thus activating the diaphragm during sleep.

- A recent RCT of 151 pts with CSR-CSA had TPNS devices inserted and were randomized to have the stimulator activated or remain inactive.

- Costanzo et al noted a significantly greater proportion of subjects reaching the primary end point (>50% reduction in AHI at 6 months) with TPNS compared with the control group (51% vs 11%).


Transvenous Phrenic Nerve Stim

- Secondary outcomes were also improved with TPNS such as greater % REM sleep, lower arousal frequency, less sleepiness and an improved patient global assessment but TPNS treatment mean AHI remained high (~26 eph) as was arousal index (~25 eph) at 6 months and cardiac and ventilatory parameters were not reported.

- Mean age and BMI were 65 years and 31 kg/m², respectively, and only 64% of subjects had HF and 42% atrial fibrillation.

- Thus, cause or type of CSR-CSA (long or short CL) was not clearly stated nor described. The role of TPNS remains speculative until further data are made available.

CHF Hospital Pt Management

• Hospitalized CHF patients should have all attention placed on optimizing the CHF condition and ASV would not be considered during an episode of acute CHF with reduced EF.

• Explore protocol for empiric APAP with oximetry and at least optimize oxygenation

• Sleep specialists might be consulted for assessment of the patient before or after discharge
Multi-Centre, RCT to Assess the Effects of ASV on Survival and Frequency of Hospital Admissions in Pts With Heart Failure (HF) and Sleep Apnea (SA)-The ADVENT-HF Trial

PI= Doug Bradley MD Toronto

• 540 Pts will randomly receive regular meds OR meds plus ASV over 5 years

• Inclusion Criteria

  • CHF x 3 months with LVEF≤ 45 % on optimal medical Rx including Beta-B with no med change in 2 wks
  • Sleep apnea with an AHI ≥ 15- 75% OSA but no titration PSG
  • Primary outcome is composite outcome of death or first CV hospital admission or new onset atrial fibrillation/flutter


Multi-Centre, RCT to Assess the Effects of ASV on Survival and Frequency of Hospital Admissions in Pts With Heart Failure (HF) and Sleep Apnea (SA)-The ADVENT-HF Trial

PI= Doug Bradley MD Toronto

• Secondary outcomes

  • Time to death from any cause
  • Number of cardiovascular hospitalizations per follow-up, days alive not hospitalized, days the patient is hospitalized subtracted from the total number of study days after randomization
  • Changes in LV function and cardiac resynchronization therapy or defibrillator implantations.
  • Changes in apnea/hypopnea index
  • Changes in quality of life Minnesota living with Heart Failure Questionnaire and Epworth Sleepiness Scale

• Unrealistic expectations??
Conclusions

• ASV devices most likely to suppress periodic breathing

• Current data demands caution for ASV use in pts with CSR and active CHF with reduced LV Fnx- *Story isn’t over*

• Role of ASV treatment in patients even with severe CHF and Complex central sleep apnea patients is not contraindicated

Present Recommendations

• Pts with CSR/CSA and significantly reduced EF should not be started on ASV. Pts should likely have repeat PSG and be assessed for component of OSA that might be present and consider CPAP benefit during PSG.

• Pts with Complex Sleep Apnea may still consider either ASV or CPAP titration.

• If predominantly CSR, Pt should explore CPAP therapy, if this has not previously failed. Primary goal of suppression of CSR now controversial. BPAP ST use very unclear.

• The only other option is to consider oxygen therapy but this may be limited by present reimbursement restrictions.

