CENTRAL SLEEP APNEA AND HEART FAILURE
Central Sleep Apnea

- Sleep onset central apneas
- Hypercapnic respiratory failure
- Idiopathic central sleep apnea
- Cheyne-Stokes respiration
- Neurologic disorders and Central sleep apnea
- Complex sleep apnea
The diagram illustrates the relationship between ventilation and arterial blood gas levels (PACO2 and PaCO2). It shows the effect of a disturbance (Δ Ventilation) on the PACO2 level (PACO2 (mm Hg)) and the resulting increase in ventilation (Δ Ventilation (response)) to maintain homeostasis. The process is further modulated by a circulation delay.
Figure 100-3 Ventilatory response to disturbance ratio (loop gain) as a function of time. The ventilatory control system is characterized by sigmoidal response curves.
SDB & Heart Failure

• Heart failure (HF) affects ∼2% of the adult population in developed countries
• Rising to 10% in those over 70 years
• >50% of patients hospitalized for HF die within 5 years
• Sleep-disordered breathing (SDB) is increasingly recognized as a marker of poor prognosis in patients with HF
• 50%~75% of patients with HF have SDB
CSA in CHF

• Central sleep apnea, as Cheyne–Stokes respiration, is found in 25 to 40% of patients who have heart failure with reduced ejection fraction.

• Prevalence of central sleep apnea vs. severity of heart failure.

• Central sleep apnea is an independent risk marker for poor prognosis and death in patients with heart failure.
Interplay Between Sleep-Disordered Breathing and Heart Failure
Treatment options for patients with Obstructive sleep apnea and heart failure

- CPAP – Positive pressure prevents the upper airway from collapsing;
- Additional benefits in HF, as positive end-expiratory pressure prevents alveoli collapsing secondary to pulmonary edema;
- Benefit cardiac function (?)
- As the lack of appropriately sized randomized outcome studies, no international HF guidelines exist yet for the use of CPAP in patients with HF and OSA in the absence of daytime somnolence
Treatment options for patients with Central sleep apnea and heart failure

• **Medical therapy** - acetazolamide – to reduce AHI, may be due its respiratory-stimulating properties as well as a diuretic action

• **Nocturnal oxygen** therapy has been shown to reduce sympathetic drive and increase nocturnal oxygen saturation in CSA and HF

• A meta-analysis of the results from 97 patients demonstrated a decrease in AHI and an improvement in LVEF in those with severe CSA (with home O2 3L/min, 3 months)
CPAP in CSA with HF

• CANPAP study
• Designed to evaluate the effect of CPAP on transplant-free survival in patients with CSA and HF
• 258 patients had been randomized and followed up for >2 years
• CPAP tx result in an improved AHI (−21 ± 16 vs. −2 ± 18/h, P < 0.001), LVEF (2.2 ± 5.4% vs. 0.4 ± 5.3%, P = 0.02), 6-min walk test distance, and reduced plasma noradrenaline concentrations
CPAP for HF with CSA

A. Episodes of Apnea and Hypopnea (no. per hr of sleep)

B. Mean Oxygen Saturation (%)

C. LVEF (%)

D. Minimum Oxygen Saturation (%)

Bradley et al. NEJM 2005
CPAP for HF with CSA

Transplantation-free Survival (%)

P = 0.54

Time from Enrollment (mo)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>CPAP group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>128</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>104</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Bradley et al. NEJM 2005
CPAP CSA suppressed vs. unsuppressed

Arzt et al. Circulation 2007
CPAP CSA suppressed vs. unsuppressed

- Baseline
- 3 mo

P = 0.984
P < 0.001, P = 0.006
P = 0.409, P < 0.001, P = 0.678

LVEF [%]

Control, CPAP-CSA-suppressed, CPAP-CSA-unsuppressed
CPAP CSA suppressed vs. unsuppressed

Arzt et al. Circulation 2007
ASV

- Adaptive servo-ventilation is a therapy that uses a noninvasive ventilator to treat central sleep apnea by delivering servo-controlled inspiratory pressure support on top of expiratory positive airway pressure.

- To investigate the effects of adaptive servo-ventilation in patients who had heart failure with reduced ejection fraction and predominantly central sleep apnea.
The ASV algorithm

- Ventilation to a moving target
- Continuously calculates a target ventilation
- Based on respiratory rate and tidal volume, the target is 90% of the patient’s recent average ventilation
Patient/machine synchronization

• Minimal support during stable breathing

![Graph showing pressure (cm H₂O) over time with annotations for pressure support and end expiration pressure.]

Pressure support = 3 cm H₂O
End expiration pressure = 5 cm H₂O

Comfortable, minimal pressure support when breathing is stable

• The underlying end expiration pressure (EEP) is clinician adjustable from 5 to 10 cm H₂O, helps reduce obstructive events and can also reduce central events.
Support when it’s needed

ASV algorithms respond to central hypopnea/apnea

ASV pressure support (cm H₂O)

Normal breathing effort

Central Apnea (no spontaneous effort)

Respiratory flow to the patient

Time

Pressure support = 10 cm H₂O
End expiration pressure = 5 cm H₂O
Adaptive support when breathing resumes

ASV pressure support (cm H₂O)

Respiratory flow to the patient

Time

Reduction in respiratory effort

Resumption of respiratory effort

ASV responds when breathing effort resumes
The ASV algorithm stabilizes patient breathing

VPAP Adapt SV responds to APNEA by increasing support.
ASV Effect on CSA

![Central Apnea Index Graph](image)

- **Control** vs Control: *P* < 0.001
- **Oxygen** vs Control: *P* < 0.001
- **CPAP** vs Control: *P* < 0.001
- **Bilevel** vs Control: *P* < 0.001
- **ASV** vs Control: *P* < 0.001

- **Control** vs ASV: *P* < 0.001
- **Oxygen** vs ASV: *P* < 0.001
- **CPAP** vs ASV: *P* < 0.001
- **Bilevel** vs ASV: *P* = 0.02
- **ASV** vs ASV: *P* < 0.001
METHODS

• Randomly assigned 1325 patients with a LVEF of \( \leq 45\% \) and moderate to severe (\( \text{AHI} \geq 15/\text{h}, \) predominantly) CSA
• To receive guideline-based medical treatment with adaptive servo-ventilation or guideline-based medical treatment alone (control)
METHODS

• 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),
• Unplanned hospitalization for worsening heart failure.
Study Patients

• 22 years of age or older and had symptomatic chronic heart failure and reduced ejection fraction

• LVEF of 45% or less, NYHA class III or IV heart failure or NYHA class II heart failure with at least one heart failure–related hospitalization within the 24 months before randomization

• had predominantly central sleep apnea (AHI, \(\geq 15\) /h, with \(>50\)% central events [apnea or hypopnea]) and a central AHI of \(\geq 10\) /h
Intervention

- Expiratory positive airway pressure, 5 cmH₂O; minimum pressure support, 3 cmH₂O; and maximum pressure support, 10 mH₂O
- The expiratory positive airway pressure was increased manually to control obstructive sleep apnea
- The maximum pressure support was increased to control central sleep apnea
Intervention

• For at least 5 hours per night, 7 days per week

• Adherence to therapy- defined as the use of ASV for an average of at least 3 hours per night.

• The target was to reduce the AHI < 10/h within 14 days after starting adaptive servo-ventilation.
Follow-up

- Clinic visits took place at study entry, after 2 weeks, at 3 and 12 months, and every 12 months
- Patients were contacted by telephone at 6 months and then at 12-month intervals
1325 Patients underwent randomization

1325 Were included in the intention-to-treat analysis

659 Were assigned to receive control therapy
   655 Received control therapy
   4 Did not receive control therapy owing to starting ASV

73 Withdrew consent
   19 Had primary end-point event before consent was withdrawn
   54 Had no primary end-point event before consent was withdrawn
   3 Started ASV before consent was withdrawn
   8 Were lost to follow-up
   2 Started ASV before being lost to follow-up

578 Completed the study
   98 Started PAP therapy
   87 Received ASV
   8 Received CPAP
   2 Received bilevel PAP
   1 Received unspecified therapy

666 Were assigned to receive ASV
   645 Received ASV
   21 Did not receive ASV

82 Withdrew consent
   19 Had primary end-point event before consent was withdrawn
   63 Had no primary end-point event before consent was withdrawn
   2 Discontinued ASV before consent was withdrawn
   1 Was lost to follow-up

583 Completed the study
   168 Discontinued ASV
<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>
<tr>
<td>Event</td>
<td>Control (N = 659)</td>
<td>Adaptive Servo-Ventilation (N = 666)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td></td>
<td>No. of Patients (%)</td>
<td>No. of Events/Yr (95% CI)</td>
</tr>
<tr>
<td>Primary end point†</td>
<td>335 (50.8)</td>
<td>0.212 (0.190–0.236)</td>
</tr>
<tr>
<td>First secondary end point†</td>
<td>317 (48.1)</td>
<td>0.200 (0.179–0.224)</td>
</tr>
<tr>
<td>Second secondary end point†</td>
<td>465 (70.6)</td>
<td>0.405 (0.369–0.444)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>193 (29.3)</td>
<td>0.093 (0.081–0.107)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>158 (24.0)</td>
<td>0.076 (0.065–0.089)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>448 (68.0)</td>
<td>0.384 (0.349–0.421)</td>
</tr>
<tr>
<td>Unplanned hospitalization for worsening heart failure</td>
<td>272 (41.3)</td>
<td>0.164 (0.145–0.185)</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>12 (1.8)</td>
<td>0.006 (0.003–0.010)</td>
</tr>
<tr>
<td>Implantation of long-term VAD</td>
<td>10 (1.5)</td>
<td>0.005 (0.002–0.009)</td>
</tr>
<tr>
<td>Resuscitation</td>
<td>19 (2.9)</td>
<td>0.009 (0.006–0.014)</td>
</tr>
<tr>
<td>Resuscitation for cardiac arrest</td>
<td>16 (2.4)</td>
<td>0.008 (0.004–0.013)</td>
</tr>
<tr>
<td>Appropriate shock</td>
<td>65 (9.9)</td>
<td>0.033 (0.026–0.043)</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>35 (5.3)</td>
<td>0.017 (0.012–0.024)</td>
</tr>
</tbody>
</table>
**A Primary End Point**

Hazard ratio, 1.13 (95% CI, 0.97–1.31)

$P=0.10$

---

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>659</td>
<td>463</td>
<td>365</td>
<td>222</td>
<td>136</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>ASV</td>
<td>666</td>
<td>435</td>
<td>341</td>
<td>197</td>
<td>122</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>
B  Death from Any Cause

Hazard ratio, 1.28 (95% CI, 1.06–1.55)
P=0.01

Cumulative Probability of Event

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 12 24 36 48 60

Months since Randomization

No. at Risk
Control  659  563  493  334  213  117
ASV      666  555  466  304  189  97
C  Death from Cardiovascular Causes

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

Cumulative Probability of Event

Months since Randomization

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>659</td>
<td>563</td>
<td>493</td>
<td>334</td>
<td>213</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>ASV</td>
<td>666</td>
<td>555</td>
<td>466</td>
<td>304</td>
<td>189</td>
<td>97</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

• The SERVE-HF study showed that adaptive servo-ventilation therapy (ASV) effectively treated central sleep apnea.

• It did not have a significant effect on the composite end point of death from any cause, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening heart failure.
Discussion

- No beneficial effect of ASV on a broad spectrum of functional measures, including quality-of-life measures, 6-minute walk distance, or symptoms.
- Significant increase in both cardiovascular mortality and all-cause mortality in the ASV group.
Discussion

- The findings of this study contrast with evidence from smaller studies and meta-analyses that have shown improvements in surrogate markers, including the plasma concentration of BNP, LVEF, quality-of-life scores, functional outcomes, and mortality among CHF patients with reduced EF and have CSA that is treated with ASV.
Discussion

- The early and sustained increase in cardiovascular mortality seen in the ASV group in this trial was unexpected.
- The pathophysiological features of this effect?
- One possible explanation is that central sleep apnea may be a compensatory mechanism in patients with heart failure.
Discussion

- Potentially beneficial consequences of central sleep apnea, particularly Cheyne-Stokes respiration, in patients with heart failure that could have been attenuated by ASV include the resting of respiratory muscles, attenuation of excessive sympathetic nervous system activity, avoidance of hypercapnic acidosis, hyperventilation-related increases in end-expiratory lung volume, and intrinsic positive airway pressure.
Subgroup analysis that showed a positive association between the proportion of Cheyne–Stokes respiration and the adverse effect of adaptive servo-ventilation on cardiovascular mortality.
Conclusion

• In patients who had CHF with a reduced LVEF and predominantly central sleep apnea, the addition of adaptive servo-ventilation to guideline-based medical treatment did not improve the outcome.

• The risk of cardiovascular death was increased by 34%, which was sustained throughout the trial, and there was no beneficial effect on quality of life or symptoms of heart failure.

• These results were seen despite effective control of central sleep apnea during ASV therapy.