Treatment of Sleep-Disordered Breathing With Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure and Reduced Ejection Fraction (SERVE-HF)

Martin R Cowie
Professor of Cardiology, National Heart & Lung Institute
Imperial College London (Royal Brompton Hospital)

m.cowie@imperial.ac.uk
Disclosures

- Research grants administered by Imperial College London from Bayer, Boston Scientific and ResMed

- Consultancy and speaker fees from ResMed, Servier, Novartis, Pfizer, Bayer, Medtronic, Boston Scientific, St Jude Medical, Alere, Daiichi-Sankyo, Bristol Myers Squibb, Amgen, MSD, Respocardia, Sorin
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.

NEJM 2015; e-pub 1 September
Adaptive Servo-Ventilation (ASV)

- 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).
- Although algorithms employed by different ASV devices vary slightly, the principle of treatment is the same: back-up rate ventilation with adaptive pressure support.

![Graph showing patient flow, apnoea, and hypopnea with ASV overlay.]

Rationale for ASV in Heart Failure with CSA

- Small and/or uncontrolled studies (and meta-analyses) suggest multiple beneficial effects of ASV on surrogate markers in heart failure (HF) patients with central sleep apnoea (CSA):¹-⁵
  - Improvements in LVEF, plasma BNP levels, quality of life and functional outcomes
- Post-hoc data from a randomised trial (CANPAP; N=258) suggest that CPAP might improve mortality when CSA is controlled (AHI <15/h) in HF patients with CSA and EF <40%⁶

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: Design

- 91 centres in 11 countries (Germany, France, UK, Sweden, Australia, Denmark, Norway, Czech Republic, Finland, Switzerland, Netherlands)
- Randomized, parallel, event-driven design
- Guideline-based medical management:
  - Alone (control group)
  - Plus ASV (Auto Set CS™, ResMed)
- ASV titration in hospital (PG or PSG)
  - Starting at default settings
  - Expiratory positive airway pressure manually increased to control obstructive sleep apnoea (OSA) and maximum pressure support increased to control central sleep apnoea (CSA)

SERVE-HF: Endpoints

• Primary composite endpoint:
  – Time to 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 unplanned hospitalization for worsening chronic HF
  – Time to death (all-cause)
  – Time to cardiovascular death
  – Change in NYHA class
  – Change in 6MWD
  – Quality of life

*C: heart transplant, long-term ventricular assist device, resuscitation of sudden cardiac arrest, or appropriate ICD shock
SERVE-HF: Patients

Inclusion Criteria
- Age ≥22 years
- Chronic stable HF (ESC guidelines, no hospitalization within 4 weeks)
- LV systolic dysfunction
  - LVEF ≤45%
- NYHA class III or IV
  - Or NYHA class II with ≥1 hospitalization for HF in previous 24 months
- Predominant CSA (AHI >15/h with ≥50% central events and central AHI ≥10/h)

Exclusion Criteria
- Significant COPD
- Oxygen saturation <90% at rest during the day
- Current use of positive airway pressure therapy
- Cardiac surgery or resynchronization therapy within the previous 6 months
- TIA or stroke in previous 3 months
- Significant valvular heart disease
- Contraindications to ASV

1325 patients enrolled between Feb 2008 and May 2013

## SERVE-HF: Baseline

<table>
<thead>
<tr>
<th></th>
<th>Control (n=659)</th>
<th>ASV (n=666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69.3±10.4</td>
<td>69.6±9.5</td>
</tr>
<tr>
<td>Male</td>
<td>90.0%</td>
<td>89.9%</td>
</tr>
<tr>
<td>NYHA class III or IV, n (%)</td>
<td>70.3%</td>
<td>70.5%</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>32.5±8.0</td>
<td>32.2±7.9</td>
</tr>
<tr>
<td>Ischaemic HF aetiology, n (%)</td>
<td>57.0%</td>
<td>59.7%</td>
</tr>
<tr>
<td>Implanted device, n (%)</td>
<td>55.2%</td>
<td>54.5%</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>59.3±20.8</td>
<td>57.8±21.1</td>
</tr>
<tr>
<td>Six-minute walk distance, m</td>
<td>337.9±127.5</td>
<td>334.0±126.4</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>91.5%</td>
<td>92.0%</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>92.7%</td>
<td>91.9%</td>
</tr>
<tr>
<td>Antiarrhythmics, n (%)</td>
<td>13.5% [p=0.005]</td>
<td>19.2%</td>
</tr>
</tbody>
</table>

Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].
Adherence and CSA Control

• ASV effectively controlled sleep-disordered breathing:
  – Mean AHI 31.2/h at baseline, decreased to 6.2–6.8/h during 48 months’ treatment (p<0.001 vs baseline)
  – Mean central AHI 25.2/h at baseline, decreased to 3.2–4.0/h during 48 months’ treatment (p<0.001 vs baseline)
  – Mean ODI 32.1/h at baseline, decreased to 8.6–9.9/h during 48 months’ treatment (p<0.001 vs baseline)

• ASV usage for an average of 3 h/night in 60% of patients
  – Usage rates constant over time (mean 3.9 and 3.7 h/night at 3 and 48 months, respectively)
Primary Endpoint: Neutral

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

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

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>659</th>
<th>463</th>
<th>365</th>
<th>222</th>
<th>136</th>
<th>77</th>
</tr>
</thead>
<tbody>
<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>

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

HR 1.28, 95% CI 1.06–1.55; P = 0.01

Cumulative incidence rate (%)

Months since Randomization

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ASV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>659</td>
<td>666</td>
</tr>
<tr>
<td>12</td>
<td>563</td>
<td>555</td>
</tr>
<tr>
<td>24</td>
<td>493</td>
<td>466</td>
</tr>
<tr>
<td>36</td>
<td>334</td>
<td>304</td>
</tr>
<tr>
<td>48</td>
<td>213</td>
<td>189</td>
</tr>
<tr>
<td>60</td>
<td>117</td>
<td>97</td>
</tr>
</tbody>
</table>

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
Control 659 563 493 334 213 117
ASV 666 555 466 304 189 97
Symptoms and Quality of Life

• No significant differences in QoL between ASV and control groups
  – Minnesota Living with Heart Failure Questionnaire
  – EuroQol-5D

• No significant difference in NYHA functional status between ASV and control groups throughout trial

• Decreased exercise capacity in ASV recipients
  – 6MWD declined in both groups, but to a greater extent in the ASV group (p=0.04)

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

• Addition of ASV to guideline-based medical management does **not** improve outcomes in patients with HFrEF and predominant CSA, *despite effective control of CSA*
  – Inconsistent with results in previous studies
  – Pathophysiology of the increased cardiovascular mortality remains to be elucidated

• 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].