Adaptive Servo-Ventilation (ASV) and Central Sleep Apnea
Focus Conference Fall 2018
Objectives

- Review central sleep apnea pathophysiology
- Understand the clinical indications for Adaptive Servo Ventilation therapy
- Learn how ASV helps to stabilize breathing
- Examine pathways to ASV for patients with CSA
- Review current clinical evidence for ASV therapy
Central Sleep Apnea Pathophysiology
Central Sleep Apnea

- Central sleep apnea (CSA) is characterized by a lack of drive to breathe during sleep, resulting in repetitive periods of insufficient ventilation and compromised gas exchange.

- These nighttime breathing disturbances can lead to important comorbidity and increased risk of adverse cardiovascular outcomes.

- CSA is considered to be the primary diagnosis when ≥ 50% of apneas are central in origin.

- Unstable ventilatory control during sleep is the hallmark of CSA.

References:
- International Classification of Sleep Disorders – ICSD3. AASM 2014
If CO₂ is too high, then the respiratory center increases respiration to blow off CO₂.

- Transmission nerve impulses activates/inhibits muscles of respiration
- Chemoreceptors (in arteries) measure O₂, CO₂, PH
- Sends message of levels to brain

Any condition that:
- Impairs the proper reading of blood gases (medication, drugs)
- Impacts the delivery of the reading to the respiratory center (Hypertension, heart failure)
- Damage of respiratory center (stroke, trauma)

...may cause central apneas
In all individuals, there is a required level of CO$_2$ in the body necessary to drive ventilation.

- Not necessarily the same in all healthy individuals and may not be constant over time.

- If breathing increases to the point where the CO$_2$ drops below this required level, breathing will cease for a short period until the CO$_2$ level has risen again (an apnea will occur).

- Most healthy individuals will have one or two central apneas during the night.
Central apneas occur below the apneic threshold on a graph showing PaCO₂ (mmHg) values.
• Decreased respiratory drive with a small fall in ventilation and rise in carbon dioxide (CO2)
• Small reductions in tidal volume are compensated by an increase in breath rate
• Alterations in respiratory system mechanics
  o Increased upper airway resistance
  o Altered chest wall mechanics
• Depressed arousal responses to chemical stimuli
Pathophysiology of CSA

• Unstable Ventilatory Control

CSA syndromes are classified in two groups according to the wakefulness CO$_2$ levels (arterial PCO$_2$).

1. **Normocapnic spontaneous central sleep apnoea/hypopnoea.**
   - Normal or low arterial PCO$_2$ when awake and an over response to hypercapnia when asleep
   - Cheyne-Stokes breathing, Idiopathic Central Sleep Apnea and Complex Sleep Apnea

2. **Hypercapnic central sleep apnoea and hypopnoea.**
   - Abnormal central pattern generator output (“won’t breathe”)
   - Impairment of respiratory motor output (“can’t breathe”)
   - Associated with hypoventilation

Eckert DJ et al. *Chest* 2007
Prevalence of CSA

- Prevalence of CSA vary greatly between the various forms
  - Eg: Most healthy individuals will have periodic breathing on high altitude\(^1\)
    - Idiopathic CSA is relatively uncommon (5% of patients referred to a sleep lab)\(^2\)
    - Treatment-emergent CSA is in approximately (3-10%) of obstructive sleep apnea titration studies\(^3\)

- High prevalence of CSA existing in patient sub-groups
  - 6.5% SDB patients have complex sleep apnea\(^3\)
  - 24% opiate patients exhibit central sleep apnea\(^4\)
  - 31% patients with HFpEF have central sleep apnea\(^5\)

- More prevalent in older individuals than in the middle aged population\(^6\).

- CSR-CSA is also more common in men and extremely rare in pre-menopausal women. Overall prevalence in women is 0.3% compared to 7.8% in men\(^6\).

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2. Malhotra A et al. Clinical Sleep Disorders. LWW 2004
Many Patients Benefit From ASV Therapy
Adaptive Servo Ventilation

- The term “servo” is often used in reference to an automatic device that uses sensing feedback to correct the performance of a mechanism.

- Therapeutical goals of ASV are:
  - Counterbalance ventilator instability by automatically adjusting inspiratory pressure support
  - Maintain a stable minute ventilation
  - Stabilize arterial oxygen and carbon dioxide levels,
  - Reduce respiratory events
  - Address upper airway collapse
Prescribers should identify contraindicated patients prior to an ASV titration being performed.

AASMS Recommendations: ASV Therapy & Heart Failure

For patients with moderate to severe predominant central sleep apnea, use this flowchart to assess which patients should be considered for ASV.
There Is A High Prevalence Of Central Sleep Apnea In The Sleep Disordered Breathing Population

ASV therapy is safe and efficacious for certain patient groups with central breathing disorders that can sometimes be challenging to treat, such as:

- Central sleep apnea (CSA)
- Complex sleep apnea (CompSA)
- Mixed sleep apnea
- Periodic breathing

Prevalence of central breathing disorders

6.5% of OSA patients suffer from CompSA

Up to 45% of patients on opioids for chronic pain have CSA or CompSA

50-70% of ischemic stroke patients develop sleep-disordered breathing

ASV shown to be effective at treating these patient populations

Patients with Complex Sleep Apnea (CompSA) demonstrate respiratory instability even during CPAP treatment.


6.5% Of OSA Patients Have CPAP Emergent Complex Sleep Apnea*
ASV Was Shown To Be More Effective Than CPAP At Treating Complex Sleep Apnea Patients*

83% CompSA patients in intention to treat trial were able to achieve AHI < 5 using ASV…

…while only 42% were able to achieve this using CPAP

* Morgenthaler TI et al. The complex sleep apnea resolution study: A prospective randomized controlled trial of continuous positive airway pressure versus adaptive servoventilation therapy. *Sleep* 2014;37(5):927-34
ASV was shown to reduce respiratory events (AHI, CAI and AI) in opioid-induced CSA better than bilevel ST*

ASV Algorithm in Summary

Components of ASV Devices

- Auto EPAP
- Auto PS
- Auto back up rate

= ASV

EPAP: expiratory positive airway pressure
HCSB: Hunter Cheyne-Stokes breathing
PS: pressure support.

Modified from Javaheri S et al. *Chest* 2014
1. ASV Creates a Target Ventilation

- Target MV is set to **90% of the patient’s recent 3 minute average**
- Target MV is **continually adjusted** to reflect changes in patient’s own MV during the night and through various sleep stages.

![3-minute moving window](image)
2. ASV Responds Quickly – Stabilizing Ventilation

- Prevents under and over ventilation by dynamically increasing (for hypopneas) or decreasing (for hyperpneas) inspiratory pressure support (PS)
If the upper airway is collapsed, no matter how advanced your algorithm is, it **CANNOT** stabilize ventilation.

### 2. ASV Responds Quickly – Stabilizing Ventilation

<table>
<thead>
<tr>
<th>ASV : 2 options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASV mode</strong></td>
</tr>
<tr>
<td>Manually set EPAP to protect airway against collapse</td>
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</tbody>
</table>
**Minute ventilation**: the volume of air which can be inhaled in one minute.

- Minute ventilation is calculated by multiplying the tidal volume and by the respiratory rate.

- The higher the minute ventilation the more carbon dioxide (CO$_2$) the person is releasing. The converse is the lower the minute volume the lower the amount of (CO$_2$) the person is releasing.

- A normal minute ventilation is about **5–8 liters** per minute.
What Studies Show About ASV Therapy And Contraindications
American Academy of Sleep Medicine has considered many studies.

AASM recommend that until further data are available, other ASV devices not be prescribed for the subgroup of heart failure patients with an ejection fraction ≤ 45% and moderate or severe central sleep apnea.\(^{16}\)

The ASV contraindication should not be generalized to other types of heart failure.*

Key Points:

- Primary endpoint of SERVE-HF was neutral.\(^\text{12}\)

- All-cause and cardiovascular mortality were significantly higher in the ASV group than in the control group “indicating ASV therapy should not be used to treat [moderate to severe] predominant CSA in patients with symptomatic heart failure and reduced ejection fraction (LVEF ≤ 45%).”\(^\text{12}\)

- The study showed that ASV therapy effectively controlled central sleep apnea.\(^\text{12}\)

- Sixty-percent of patients randomized to ASV therapy used it for at least three hours per night.
ASV devices peaked at 79% of complex sleep apnea patients in 1Q14, use of the ASV devices has steadily declined to 55% of patients in 1Q16.*

Decline presumed to be driven by the results of SERVE-HF trial

* http://www.sleepreviewmag.com/2016/05/first-quarter-2016-sleep-center-survey-results/
Importantly, this illustrates certain patients may not be getting the therapy they need to normalize their AHI.
The contraindication does not apply to all patients, as stated by Dr Holger Woehrle, VP Clinical Research and Medical Director of ResMed Europe and Asia Pacific*

“While this was an unexpected result, the findings remain vitally important for the heart failure community and for patients with chronic heart failure, reduced ejection fraction and predominant central sleep apnea. It is important that we do not extrapolate these findings beyond the specific population and parameters that were investigated in SERVE-HF. The results cannot, and should not, be applied to people with CSA in the absence of systolic heart failure, or to people with obstructive sleep apnea (OSA) with or without chronic symptomatic heart failure.”

Multicenter, randomized controlled Phase II clinical trial in HF patients with HFpEF (LVEF > 45%) or HFrEF (LVEF ≤ 45%) and an AHI ≥ 15 events/hr

Hypothesis:
• Evaluate the cardiovascular outcomes of ASV following ADHF hospitalization

Recruitment was stopped early due to SERVE-HF safety concerns in HF patients with (LVEF) ≤ 45% and predominant central sleep apnea.

Up To 29.5% Of Patients With Heart Failure And Preserved Left Ventricular Ejection Fraction Have CSA*

Studies have shown benefit using ASV therapy to treat SDB patients who have heart failure and preserved ejection fraction11

ASV therapy is contraindicated in patients with chronic, symptomatic heart failure (NYHA 2-4) with reduced left ventricular ejection fraction (LVEF ≤ 45%) and moderate to severe predominant central sleep apnea.

CAT-HF sub-group analysis showed statistically significant improvement among HF patients with LVEF > 45% (HFpEF) and SDB (AHI ≥ 15)**

* Bitter T et al. Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. Eur J Heart Fail. 2009

ASV Indication for Use
ASV is indicated for the treatment of patients weighing more than 66 lb (30 kg) with obstructive sleep apnea (OSA), central and/or mixed apneas, or periodic breathing.

Overall, the primary endpoint comparison was neutral (p-value = 0.89)

Sub-group analysis showed statistically significant improvement in the primary endpoint among patients using ASV with LVEF > 45% (HFpEF) and SDB (AHI ≥ 15) (p-value = 0.045)

ASV Contraindication
ASV therapy is contraindicated in patients with chronic, symptomatic heart failure (NYHA 2-4) with reduced left ventricular ejection fraction (LVEF ≤ 45%) and moderate to severe predominant central sleep apnea.

Prescribers should identify contraindicated patients prior to an ASV prescription being written.