Central Sleep Apnea
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Understanding Central Sleep Apnea (CSA):
Objectives

• Define Central Sleep Apnea
• Recognize Risk factors and Clinical Presentation of CSA
• Describe How to Diagnose CSA
• Outline Different Types of CSA and how to treat them

Definition of a Central Apnea
Repetitive cessation or decrease of both airflow and ventilatory effort during sleep for at least 10 seconds
Obstructive Sleep Apnea (OSA) vs. Central Sleep Apnea (CSA)

OSA is a disease of upper airway collapse
“The train tunnel collapses”

CSA is a disease of respiratory signal control
“There is no signal for the train to go”

OSA is more common than CSA:
A little less than 1% of patients > 40 years old found to have CSA
Estimates for OSA by age:
- 40-50 years old = 10%
- > 50 years old = 10-25%

Also, CSA less studied than OSA: Literature Review (Pubmed) Jan 2017 to present = CSA vs OSA: 53 vs 1892 Articles

CSA Epidemiology
CSA estimates to be nearly 1% in patients > 40 years: overall prevalence of CSA on PSG = 0.9 %
- OSA prevalence depending on age at least 10 times higher than CSA
- But this number does not take into account those patients with Mixed Sleep Apnea or a combination of both Central and Obstructive events which is a common problem
- CSA and Mixed Sleep Apnea are challenging to treat, probably more so than OSA alone
- 1% of patients > 40 years does NOT take into account much higher rates of CSA in patients who are older with other medical problems such as CHF = CSA is more common among patients with CHF.
CSA Epidemiology, continued

• Approximately 50% CSA cases were associated with Cheyne-Stokes breathing (more on Cheyne-Stokes later)

• The median age of patients with CSA was 69 years.

• In patients > 65, prevalence of CSA three times higher than younger patients

• CSA was more seven to nine times common in men than women

CSA Risk Factors

So who develops Central Sleep Apnea?

• Older
• Male
• CHF
• Takes Opioids
• Lives at Altitudes > 4500 feet
• CVA
• Atrial Fibrillation

A patient commonly seen in the Montana Veteran population! CSA is more common than we think!!

CSA Symptoms/Complaints

Similar to OSA
• disrupted sleep and poor sleep quality
• excessive daytime sleepiness
• insomnia
• inattention, and poor concentration
• nocturnal dyspnea*
• morning headaches
• nocturnal angina
Correlates and consequences of central sleep apnea in a national sample of US veterans. Sleep. 2018 Sep 1;41(9).

The prevalence and consequences of central sleep apnea (CSA) in adults are not well described. Utilized large Veterans Health Administration (VHA database, evaluated the incidence, clinical correlates, and impact of CSA on healthcare utilization in Veterans.

Analysis of a retrospective cohort of patients with sleep disorders was performed from outpatient visits and inpatient admissions from fiscal years 2006 through 2012.

The CSA group was compared with a comparison group.

The number of newly diagnosed CSA cases increased fivefold during this timeframe.

Veterans with CSA were at an increased risk for hospital admissions related to cardiovascular disorders compared with the comparison group (incidence rate ratio [IRR] = 1.50, 95% CI: 1.16‐1.95, p = 0.002).

Additionally, the effect of prior HF on future admissions was greater in the CSA group (IRR: 4.78, 95% CI: 3.87‐5.91, p < 0.0001) compared with the comparison group (IRR = 3.32, 95% CI: 3.18‐3.47, p < 0.0001).

Thus, CSA in veterans is associated with cardiovascular disorders, chronic prescription opioid use, and increased admissions related to the comorbid cardiovascular disorders.

CSA Diagnostic Criteria

- PSG is required
- Home testing has NOT been validated as a tool to evaluate CSA
- Different Kinds of CSA all have the following in common
  - Central AHI ≥5 on PSG
  - ≥50 percent of the total number of apneas and hypopneas are Central
  - The patient is symptomatic with: sleepiness, awakening with shortness of breath, snoring, witnessed apneas, or insomnia or nonrestorative sleep.
  - The disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder.

CSA Diagnostic Criteria, continued:

- Primary CSA
  - There is no evidence of Cheyne-Stokes breathing.
  - There is no evidence of daytime or nocturnal hypoventilation.

- Cheyne-Stokes CSA
  - At least three consecutive central apneas and/or central hypopneas separated by crescendo-decrescendo breathing with a cycle length of at least 40 seconds (ie, Cheyne-Stokes breathing pattern)
  - The breathing pattern is associated with atrial fibrillation/flutter, congestive heart failure, or a neurological disorder.
CSA Diagnostic Criteria, continued:

- Medication Induced CSA
  - The patient is taking an opioid or other respiratory depressant

- High Altitude CSA
  - Recent ascent to a high altitude > 5000 feet.
  - Symptoms are clinically attributable to high-altitude periodic breathing or seen on PSG

Central Sleep Apnea is...

Characterized by unstable control of ventilation

A complex interplay between the Respiratory Control Center in the Brainstem and Gas exchange and in particular CO2

Categories of Central Sleep Apnea

- Physiologic
- Hyperventilation (hypocapnic = Low CO2)
- Hypoventilation (hypercapnic = High CO2)
- Positive Airway Pressure Induced
CSA: Normal Physiologic

Normal Physiologic Central Apneas we do not “treat” and they occur with:

- Sleep onset
- Post-arousal
- Post-Sigh
- Phasic Rem Sleep

CSA Hyperventilation/Low CO2: will discuss the following

- CHF
- Stroke
- High Altitude Induced CSA
- ? Treatment/PAP induced CSA

CSA: Hyperventilation/Low CO2

Hyperventilation leading to Hypocapnia (Low CO2): most common accounts for more than 50% of CSA

- Cheyne Stokes Breathing Pattern - crescendo-decrescendo respiratory pattern
  - NOT seen during REM sleep
- Related to CHF, Atrial Fibrillation and Stroke
- End Stage Renal Disease
- Idiopathic Primary Central Sleep Apnea: Less than 10% of CSA
- High Altitude (MORE ON THIS AS IMPORTANT TO MONTANA)
CSA and CHF

- Patients with CHF can have:
  - OBSTRUCTIVE Sleep Apnea – OSA
    - The usual risk factors along with Edema of the upper airway in patients with CHF airway
  - Central Sleep Apnea – with or without Cheyne Stokes Breathing
  - Cheyne Stokes Breathing is a characteristic breathing pattern of Crescendo-Decrescendo respirations
    - Can occur in Wake OR Sleep
    - In Sleep, increased arousals.
    - In sleep, Respiratory Cycle length usually 40-90 seconds

Cheyne-Stokes Breathing

Cheyne Stokes Breathing

A controller (the respiratory center) and a plant (the lungs) operate in a reciprocal relationship (negative feedback) to regulate a pCO2. The interaction between these two is dependent on the circulatory delay.
Cheyne-Stokes Breathing and CO2 dysfunction in CHF

- CHF Patients with Cheyne-Stokes have lower PaCO2 (Hypocapnia) than patients who have heart failure without Cheyne-Stokes.
- The theory is that these patients have a hypersensitive respiratory control center which causes an Apnea to increase the PaCO2.
- The apnea will last until the the Respiratory Control center detects the appropriate PaCO2 level. HOWEVER, this can be prolonged due to heart failure delay in circulation.
- With prolonged circulatory time, hypocapnia develops by the time the Respiratory control center stimulates breathing again.
- Elevated PaCO2 then causes increased respiratory rate which then leads to PaCO2 dropping too low again.
- The net effect is oscillation of ventilation between apnea and hyperpnea.

CSA treatment in the setting of CHF and CSB

- To treat or not to treat?
- CPAP may be effective in some patients but often not.
- BIPAP may be a little more effective than CPAP.
- Bleed in 02 with either CPAP or BIPAP can help decrease central events.
- ASV effective but not for everyone.
- 02 alone – sometimes the best option.

Adaptive-Servo Ventilation (ASV)

- Non-Invasive Ventilator.
- Delivers expiratory positive airway pressure with inspiratory pressure support - this is variable based on what the ASV algorithm senses the patient needs.
- Provides a Back-up Respiratory Rate if a Central Apnea i.e. OPEN airway Apnea is detected.
CSA With CHF

• SERVE-HF: Adaptive Serve-Ventilation for Central Sleep Apnea in Systolic Heart Failure (HFrEF EF < 45%); Cowie, et.al; Sept. 2015, NEJM

  • 1325 randomized, controlled patients with EF < 45% and AHI > 15 with 50% or more of apneas and hypopneas characterized as Central

  • Conclusions: patients may have felt better using ASV but all cause and cardiovascular mortality was increased.

  • MUCH discussion ensued on review of this paper and the guideline until further study done was to AVOID ASV in patients with EF < 45%

2018 Rebuttal to Serve-HF? Not quite yet...


  • Adaptive servo-ventilation to treat central sleep apnea in heart failure with reduced ejection fraction: the Bad Oeynhausen prospective ASV registry.

  • ASV prescribed to 224 patients: 48.7% ASV-treated patients and 191 (58.6%) controls died: older age, lower LVEF, impaired renal function, low sodium concentration, and nocturnal hypoxemia were significant predictors of mortality. (adjusted Cox modelling hazard ratio of 0.95, 95% confidence interval 0.68-1.24; p = 0.740)

  • Patient reported NYHA functional class improved in the ASV group, but LVEF, natriuretic peptides and blood gases remained unchanged.

  • CONCLUSIONS: Long-term ASV treatment of predominant CSA in HF-REF patients had no statistically significant effect on survival. ASV improved HF symptoms, but had no significant effects on exercise capacity, LVEF, natriuretic peptide concentrations or blood gases during follow-up as compared to control patients.

  • BUT: much smaller number of patients evaluated and p value high?

Medications for CSA with CSB associated with CHF - not tested in CVA (alphabet soup!)

• Theophylline: respiratory stimulant – no long term studies; one small study suggested a decrease of AHI from 37 to 18

• Acetazolamide:
  • carbonic anhydrase inhibitor = mild metabolic acidosis, which stimulates respiration and decreases the frequency of central apneas
  • Minimal studies in patients with CSA and no long term efficacy data

  BOTH have significant side effects
**CSA and Stroke**

- Very Common: up to 70% of patients developed ANY kind of Sleep Apnea (apnea-hypopnea index >10) within the initial 72 hours after CVA.
- 26% CSA with Cheyne-Stokes breathing.
- Interestingly, 3 mo post CVA, CSA was detected in only 7 percent of the patients.
- There was no relationship between the location of the stroke and the likelihood of sleep apnea.

**Treating CSA and Stroke**

- CPAP
- BIPAP
- O2 bled in or on its own
- ASV
- Treatment challenges with mask fit and aspiration prevention
- Re-assessment important

**What do you do if the patient has both OSA and CSA? Mixed Sleep Apnea**

- Can be a treatment challenge!
- OSA may cause central apneas with disruption of the usual breathing pattern and respiratory arousals adding to central apneas.
- Try to correct the obstructive events at the lowest possible PAP needed.
- If Central Apneas develop on PAP, consider decreasing the PAP level.
  - CSA seems more prevalent at PAP > 14 cm.
Mixed Sleep Apnea, continued

• Worse when supine – try to avoid Supine sleep with positional aid
  • Unclear why CSA worse supine. Theory:
    • Reduction in Cardiac output causes delay of blood gas information from the pulmonary
    capillary bed to the brainstem chemoreceptors leading to central apnea

• Bleed 02 into PAP?
• Bipap vs. CPAP?
• ASV (if LVEF > 45%)

High Altitude induced CSA

• Respiratory cycle length is short = 12-34 seconds
• More prevalent above 5000 feet but some patients who are sensitive to hypoxia can occur at lower altitudes and last longer
• Increases with increasing altitude
• Hypoxia causes hyperventilation and subsequent hypocapnia
  • Low 02=Increase RR=low CO2
  • Hypocapnia alkalosis induces central apnea
Acute High Altitude CSA Treatment

- Descend to lower Altitude
- O2
- CO2

Living at High Altitude

- Technically not High Altitude CSA because theoretically the patient is supposed to be acclimated
- BUT, for those patients with underlying cardio-pulmonary disease, it appears that these patients DO have what appears to be central apnea from living at high altitude
- Adding O2 resolves many of the central apneas
  - Complex interplay between O2, CO2 and ventilation
- Vacationing to lower altitude, centrals resolve
- Definitely an important considering for patients in Montana
  - The Sleep Lab Altitude vs. the Home Altitude

PAP induced CSA
CSA as a response to PAP

- Unclear etiology? May be related to Hypocapnia, especially if poor mask fit, high leak, high dead space?
- Approximately 10% of patients
- Most resolve with time on PAP
- Some do not in which case ASV is the treatment of choice
- Mask fit is KEY!
- Positional therapy i.e. avoiding supine sleep may be helpful

Treatment-Emergent Central Sleep Apnea (TECSA)

- Ann Thorac Med. 2018 Apr-June: Natural history of treatment-emergent central sleep apnea on positive airway pressure: A systematic review.
- TECSA is observed in some patients when they are treated with positive airway pressure (PAP) after significant resolution of the preexisting obstructive events in patients with obstructive sleep apnea. The objective of this study was to systematically review the literature for studies describing the natural history of TECSA.
- Five studies were identified that discussed the natural history of TECSA.
- Overall, TECSA developed in 3.5%–19.8% of PAP-treated patients with OSA.
- The vast majority will experience complete resolution of central apneas over a few weeks to months.
- Approximately, 1/3 of patients with TECSA may continue to exhibit persistence of central sleep apnea on reevaluation.

Treating TECSA

- Wait
- CPAP, BiPAP, BiPAP ST (back-up rate)
- ASV most effective
- Make sure mask fits!
Opioids and CSA

CSA: Hypoventilation/High CO2

Hypoventilation leading to Hypercapnia (High CO2)

- Opioid use
- Nervous system diseases
  - such as tumors or Arnold-Chiari malformations which affect the brainstem or spinal cord
  - MS or other Neurodegenerative diseases
- Neuromuscular diseases
  - Myotonic dystrophy
  - ALS
  - Guillain-Barré
- Severe pulmonary mechanical abnormalities: kyphoscoliosis
- Congenital Central Hypoventilation Syndrome

Opioid Induced CSA:

Hypoventilation with Hypercapnia

Opioid Epidemic

- CDC: 1999-2017, nearly 400,000 deaths from Opioid overdoses (illicit and prescription)
- In 2017, the number of deaths from Opioids was 50x times higher than in 1999
- On Average, 130 Americans die every day from an Opioid overdose
CSA and the Opioid Epidemic: is there a connection?

- Deaths associated with Opioids:
  - Most often found in the morning
  - Most often occur in bed
  - Respiratory Depression is the most common cause of death in Overdoses
  - Timing and location of deaths suggest occurring during sleep
  - Suggests a strong Association of Ataxic Breathing induced by opioids and respiratory depression associated with sleep disordered breathing

Effects of Opioids on Respiration: wake or sleep

- Dose dependent effect – the higher the dose, the more effect
- Decreased respiratory rhythm drive: respiratory pacemaker in the brainstem is inhibited by activation of Opioid receptors.
- Cannot uncouple Analgesia from Respiratory effects (this includes Buprenorphine)
- Decreased Diaphragm muscle activity, decreases hypoglossal nerve activity = increased obstructive apnea
- Decreased Chemoreceptor response to Hypoxia and Hypercapnia with narcotics so usual amount of hypoxia and/or hypercapnia which would stimulate breathing is “ignored”

Opioid Effect on Respiration in Sleep

- Central Apnea
- Obstructive Apnea: loss of upper airway tone
- Hypopneas: partial loss of airflow associated with O2 desaturation
- Ataxic breathing (Biot’s)
- Bradypnea – decreased respiratory rate
- Hypoxemia
- Reduced arousal response
- REM suppression
**Ataxic Breathing or Biot’s Breathing: sleep breathing with the use of opioids**

- Breaths have irregular tidal volume and frequency, interspersed with central pauses
  - Patients compared and matched for age, sex and BMI:
    - Patient with OSA alone
      - AHI 30.2, Central Apnea Index 2.1
    - Patients with OSA and taking Opioids
      - AHI 43.5 with a Central Apnea Index of 12.5

**Opioid Induced CSA: Treatment**

- Opioid reduction or cessation: ideal but not always possible
- Adaptive Servo-Ventilation (ASV)
- CPAP does NOT work
- O2 does NOT work and can further induce respiratory depression
### Summary of CSA definition

- Repetitive cessation or decrease of both airflow and ventilatory effort during sleep for at least 10 seconds
- Characterized by unstable control of ventilation
- A complex interplay between the Respiratory Control Center in the Brainstem and Gas exchange and in particular CO2

### Summary of Types of CSA

- Physiologic
- Hyperventilation (hypocapnic = Low CO2)
- Hypoventilation (hypercapnic = High CO2)
- Positive Airway Pressure Induced *may be hypocapnic—not sure

### Summary of Treatment of CSA

**It Depends on the cause and the type of CSA: Address the associated medical condition first!**

- Cheyne-Stokes Breathing with Preserved Ejection Fraction- ASV
- Cheyne Stokes Breathing with Reduced Ejection Fraction – BiPAP + O2 or O2 alone
- Mixed Sleep Apnea – sometimes CPAP alone will resolve the obstructive events which then resolve the associated central events
- High Altitude – Descend and/or O2
- Opioid CSA – dose reduction/cessation or ASV
- Treatment induced CSA – wait – most will resolve and if not, ASV
References

- Opioid-Induced Central Sleep Apnea, Tom Cloward, MD, Intermountain Health Care, SLC, Utah.
- SERVE-HF: Adaptive Servo-Ventilation for Central Sleep Apnea In Systolic Heart Failure(HF-ET EF < 45%); Coste, et al. Sept. 2015, NEJM.

THANK YOU! Sweet Dreams!