Advanced Titration Strategy for Heart Failure

CASE PRESENTATION and DISCUSSION

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Current Concepts in Sleep Medicine
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Conflict of Interest

• None
Case Presentation:

Summer/Fall 2014: New patient consultation

CC: Nocturnal dyspnea & fatigue; family concerned for OSA

HPI: 72 year old man experiencing symptoms of sleep disordered breathing: STOP-BANG score 6
- Fatigue (FSS 54) with some daytime sleepiness (ESS 9) when sedentary
- Witnessed apneas with gasping arousals from sleep (maximum of 4 times a night)
- Used to snore nightly and loudly; still snores, but softer than 10 years prior
- Interrupted, unrefreshing sleep (2-3 awakens per night due to gasping arousals & to use bathroom)
- AM dry mouth, no morning headaches
- Denies orthopnea and paroxysmal nocturnal dyspnea
- Diagnosed about a decade prior with OSA (~2004), unable to tolerate CPAP (previous study not available); but now willing to reconsider PAP therapy with encouragement of his family
Case Presentation:

PMHx:

- Prior smoker, tobacco dependence in remission
- GERD
- BPH, ED, Bladder stone s/p cystolithotripsy (2008)
- Extensive cardiovascular history:
  - LAD myocardial infarction (1976, 1985) s/p PTCA (2003) for unstable angina
  - Ischemic cardiomyopathy (EF 35% in 2003, 40-45% in 2010 with anterolateral/apical akinesis)
  - Chronic heart failure (NYHA II), no hospitalizations for this
  - Sick sinus syndrome s/p pacemaker (2012); also has a history of Afib/Aflutter
  - Peripheral vascular disease with arterial thromboses (femoral 1976, tibial/popliteal in 2010)
  - Hypertension, hyperlipidemia
Case Presentation:

**PE:**
- Vital signs: BP 118/64 mmHg, P 60, Wt 222, Ht 68 in, BMI 33.3, O2 sat 97%
- General: Alert, conversant, in no acute distress
- Neck: Circumference 45 cm
- Heart: Regular, rate and rhythm. No murmurs, rubs or gallops.
- Lungs: Clear to auscultation bilaterally.
- Abdomen: Soft, non-tender. Active bowel sounds.
- Extremities: No clubbing, cyanosis, *trace edema*
- Neurologic: Non-focal; normal affect.

**Labs:**
- Pulmonary function testing: Within normal limits (FEV1: 3.06 L or 96% predicted, DLCO 78%)
Clinical Evaluation & Questions:

- History of obstructive sleep apnea diagnosed ~10 years ago.
- Significant cardiovascular disease

Should patient requalify for CPAP with home sleep testing or polysomnography?

Split-night polysomnography ordered because of concern for central sleep apnea in addition to known OSA

Instructions to tech: 1) Score all hypopneas as central or obstructive
2) If CAHI > 50% of events, titrate ASV therapy
Treatment for Central & Treatment Emergent Sleep Apnea

Treatment of Central Sleep Apnea (CSA) with an E0471 device requires **ALL** of the following:

- AHI > 5
- Central apneas & hypopneas > 50% of total apneas & hypopneas
- Central AHI ≥ 5
- Symptoms of sleep disturbance
  - Daytime sleepiness
  - Disrupted sleep
  - Awakening short of breath
  - Witnessed apneas
- There is significant improvement with the use of the E0471 device while patient on usual FiO2
- There is no evidence of daytime or nocturnal hypoventilation

**E0471**: Bilevel device with a back-up rate
Split-Night Polysomnography Results

**BASELINE:**

TRT: 3 hours; TST: 2.1 hours, SE: 70%
N1 7%, N2 93%, N3 & REM 0%

**AHI:** **33.8**
- OSA: 7
- CSA: 26 (Cheyne-stokes present)
- Mixed apneas: 4
- Obstruction hypopneas: 26 due to mild snoring
- Central hypopneas: 8

Lowest O2 saturation: 88%
PLMI 115.2, PLMAI 46.2
Cardiac: 3rd degree AV block despite pacemaker; wide QRS

**TITRATION:**

**CPAP Titration:** (CPAP 5 to 12 cm water pressure)
TST: 0.6 hours, SE: 38%

**AHI:** **96.7**
- OSA: 5; Mixed apneas: 22; OH: 0
- CSA: 29 (Cheyne-stokes present); CH: 2
Lowest O2 saturation: 88%

**OSAI:** 17.6
**CSAI:** 16.2

**ASV Titration:** (EPAP 5, PS 3-15 cm water pressure)
TST: 2.2 hours, SE: 94%

**AHI:** **0.9**
- OSA: 0; Mixed apneas: 0; OH: 0
- CSA: 0; CH: 2
Lowest O2 saturation: 89%

**OSAI:** 45
**CSAI:** 51.7
Medicare 31-90 Day Treatment Review

Therapy & Clinical response: ResMed ASV machine EPAP 5, PS 3-15 cm water pressure via small Simplus FFM

- Improved daytime energy levels
- No daytime napping
- No snoring or witnessed apneas, although patient had 4 episodes of gasping arousals where he felt he needed more pressure from the machine

Download information: 9/22/2014 – 10/23/2014

- ASV was used 32 out of 32 days and for 4 or more hours 100% of the time
- Average daily use is 8 hours, 4 minutes
- No large leak; Residual AHI: 2.1

Recommendations:

- Medicare verification completed
- Removed ramp, EPAP empirically increased to 6 cm water pressure to reduce air-hunger
- Cardiology considering pacemaker replacement
Meta-analysis of 10 randomized controlled trials:
• 2/10 were trials of CSA-CSR in CHF patients
• Only 4/10 used AHI to diagnosis OSA
• 6/10 studies enrolled patients who already had some degree of cardiovascular disease

Conclusions and Relevance  The use of PAP, compared with no treatment or sham, was not associated with reduced risks of cardiovascular outcomes or death for patients with sleep apnea. Although there are other benefits of treatment with PAP for sleep apnea, these findings do not support treatment with PAP with a goal of prevention of these outcomes.
Sleep Disordered Breathing in Heart Failure

- Heart failure affects more than 5.7 million Americans. *Circulation* 2016;133
- Reduced LVEF is associated with increased mortality. *JAMA* 2003; 289: 194-202
- CSA occurs in 25-40% of patients with chronic heart failure (CHF) due to left ventricular (LV) systolic dysfunction. *Ann Intern Med* 1998; 128(3): 204-207; *Sleep Med Clin* 2007;2:615-21
- OSA and CSA can occur in patients with CHF, separately or in combination
  - CHF can result in CSA-CSR with increased CSA with worsening cardiac function. *J Appl Physiol* 2005; 99: 2433-2439
- Presence of CSA, especially CSR, is associated with increased morbidity and mortality
  - Annual death rate from HF has decreased but is still >30% over 3 years. *Circ Heart Fail* 2013; 6: 4141-419
Central Sleep Apnea: 2 Basic Mechanisms

- Restrictive Lung & Neuromuscular Disease
- Obesity
- COPD
- Hypoventilation
  - Chronic Hypercapnic Respiratory Failure
- Hypoventilation via High Loop Gain
  - Hypo- or Normocapnic Central Sleep Apnea
    - Periodic Breathing & CSR
    - Treatment Emergent (CompSAS)
Respiratory Control Loop

**Input:** \( \text{CO}_2, \text{O}_2 \) concentrations
- Carotid bodies
- Mechanochemical receptors (lungs)
- Medullary chemoreceptors

**Respiratory Control Center**
- Pons and medulla oblongata

**Output**
- Phrenic nerve
- Diaphragm
- Accessory muscles

Circulation Time

Image from: Online.peralta.edu
Increased sensitivity to CO\textsubscript{2} determines the frequency and severity of CSA
- Carotid bodies
- Mechanochemical receptors (lungs)
- Medullary chemoreceptors

Increased central ventilatory responsiveness to CO\textsubscript{2} predisposes to CSA
- Pons and Medulla oblongata

Instability of the ventilatory control system due to increased autonomic nervous system sensitivity & responsiveness to pCO\textsubscript{2} and pO\textsubscript{2}
Apnea Threshold (AT)

- The $P_{a\text{CO}_2}$ level below which breathing will cease resulting in a central apnea.

- As long as the current $P_{a\text{CO}_2}$ is greater than the AT, breathing continues.

- If the $P_{a\text{CO}_2}$ drops beneath the AT, breathing ceases until CO$_2$ levels climb above the AT, then breathing resumes.
The $pCO_2$ reserve is the difference between the baseline $P_aCO_2$ and AT

- Low $pCO_2$ Reserve = greater chance of CSA
- High $pCO_2$ Reserve = less chance of CSA

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**Why are CHF patient susceptible to CSA-CSR via high loop gain?**

**Increased sympathetic tone**
- Leads to increased autonomic sensitivity to $CO_2$ and $O_2$, so patient has a lower baseline $pCO_2$

**Male gender**
- Men have ↑ chemoresponsiveness and ATs, likely related to testosterone levels

**Hypoxia & Tachypnea**
- Pulmonary congestion stimulates vagal nerve afferent fibers that increases ventilation; this drives down $P_aCO_2$

**Higher AT**
- Metabolic alkalosis raises the AT (lowers pCO2 reserve); common effect of loop diuretics

**Slow circulation time**
- Slows communication between the respiratory and autonomic systems

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![Breathing diagram](image)
Breathing Control During Sleep

During sleep:
• Tidal volume decreases so MV decreases
• Chemosensitivity to CO$_2$ and O$_2$ declines, especially during REM sleep > NREM

As a result:
• P$_{\text{aCO}}$$_2$ climbs during sleep to ~45 mmHg
• The pCO$_2$ Reserve increases
• Making CSA less likely to occur

![Graph showing Arterial PaCO$_2$ and PaCO$_2$ Reserve over different sleep stages.]
ServoVentilation

- Used to treat central sleep apnea by stabilizing high loop gain:

**Respironics BiPAP Auto-SV Advanced™:**
- Machine algorithm monitors peak flow over a 4 minute window and automatically adjusts PS based on target peak flow. *SLEEP 2011; 34(12): 1693-8*
- Machine algorithm also adjusts EPAP to stabilize the airway and adjusts back-up respiratory rate.

**ResMed ASV™:**
- Machine monitors minute ventilation (RR x TV) over a 3 minute window of time.
- Machine sets Target Ventilation at 90% of patient MV and adjusts PS based this:
  - If patient ventilation < target ventilation, PS will be provided to target ventilation.
  - If patient ventilation > target ventilation, PS will be decreased.

**Respironics Auto-SV™ (Auto-ServoVentilation)**
ASV: Adaptive ServoVentilation Therapy

Graph showing the relationship between pressure and patient arterial PaCO₂. The graph includes lines for machine support and patient effort, with markers for pCO₂ reserve and apnea threshold.
ASV Therapy

Early studies demonstrated:

• Improved LVEF by an average of 6.2%
• Reduced AHI by an average of 31%, which usually normalized the AHI to 5 or less
• Decreased arousals, decreased N2, increased REM

*SLEEP 2012; 35(1):17-40*
SERVE-HF Trial: NEJM 2015; 373 (12): 1095 - 1105

- 1325 patients, randomized to ASV (EPAP manually titrated, PS 3-15 cm water pressure)
  - Symptomatic CHF (NYHA class II-IV), EF < 45%, on medical therapy
  - CSA with AHI ≥ 15, with more than 50% due to central events, C-AHI ≥ 10
  - ASV adherence was defined as at least 3 hours per night; goal to reduce AHI to < 10 events per hour

Results:
- ASV had NO effect on:
  - Reducing cardiovascular interventions
  - Hospitalizations for decompensated CHF
  - Improving NYHA classification
  - Improving quality of life or 6 MWD

- ASV improved Epworth sleepiness scores
- Only 60% of the ASV group were able to use therapy for 3 or more hours
  - Mean AHI reduced to 6.6/hr
  - Average EPAP 5.5 cm water pressure

*Cardiovascular mortality was higher in the ASV treated group
- Especially when EF < 35% and when CSR accounted for a high percentage of events
Servo-Ventilation Therapy

Still recommended treatment for:
- Primary CSA
- Non-CSR periodic breathing (stroke, renal failure)
- Cardiac CSA with EF > 45%
- Treatment emergent CSA

But contraindicated for CSA in patients with chronic heart failure and EF ≤ 45%
- Instead use:
  - Medical optimization
  - CPAP therapy
  - Bilevel ST therapy
  - Supplemental oxygen

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

Spring/Summer 2015:

6 Month Clinic Follow-up:

Interval History:

- Doing well until late February 2015 when he developed a perforated bowel in Arizona requiring emergency colostomy
- Spent a month in rehab, where he developed insomnia & would play cards all evening
- Oxygen added to ASV there, but adapter leaked; slept better without oxygen, just ASV
- In rehab was started on Ambien 5 mg, then doxepin 3 mg; but noticed no benefit; he is not able to stay asleep for more than 6 hours
- Aside from insomnia (new ASV download corroborates this), he is back to his baseline health and considering surgery for a colostomy reversal later in the summer

Download information: 2/18/2015 – 5/18/2015

- ASV was used 84 out of 90 days and for 4 or more hours 73% of the time
- Average daily use is 5 hours, 53 minutes
- No large leak; Residual AHI: 2.2 (same as prior)
Case Presentation:

Spring/Summer 2015:

6 Month Clinic Follow-up:

Discuss SERVE-HF Trial findings:

- Echo was repeated 5/13/2015: EF 25-30% with akinesis of the anteroseptal and apical walls. Diastolic dysfunction present with moderate left atrial enlargement
  - Lisinopril 5 mg daily
  - Carvedilol 3.125 mg x 2 tablets BID
  - Spironolactone 25 mg, ½ tablet daily
  - Lasix 40 mg daily
- Already scheduled to have a new bi-ventricular pacemaker placed with AICD placed in June
- Ambien CR 6.25-12.5 mg
- Opted to stop ASV therapy
- Since CPAP 8 cm water pressure resolved obstructive events during the prior PSG, he opted to use CPAP as a bridge until CRT/AICD; then will re-titrulate CPAP, oxygen +/- Bilevel ST therapy 1 month after pacemaker placement (he stopped CPAP 3 days later, because it worsened his sleep)
Medical Management of Heart Failure

**β-blockers**

- Early studies with metoprolol and bisoprolol did not show a survival benefit; meta-analysis with carvedilol revealed a 52% reduction in mortality (9 to 4.5%) *J Am Coll Cardiol* 1997; 30(1): 27-34
  
  1. Carvedilol 1.25 mg BID, increasing to 10 mg BID or maximal tolerated dose (n=16) *Circ J* 2009;73:295-8
    - Stable CHF (NYHA II or III), EF < 50%; with predominantly central events, CAI > 5
    - AHI (34 → 14) and CAI (13 → 1.9) reduced in a dose dependent manner, but worsened OAI (1.1 → 3.1); EF increased (32 → 45%)
    - There were 31% on carvedilol that continued to have CSA-CSR
  
  2. Carvedilol (n=27) versus none (n=18) *CHEST* 2007; 131:130-5
    - AHI lower with β-blocker 14 vs 33, CSA lower 1.9 vs 11; CAI dropped to < 5 in those with carvedilol doses ≥ 10 mg daily; EF did not change

Proposed mechanism(s)

- Diminish central chemosensitivity to CO2; reduce vagal afferent nerve stimulation caused by pulmonary congestion (thus reducing tachypnea and hyperventilation)
- Improved LF function and CO, improved circulation time (which reduces the length of the hyperpneic phase and total periodic breathing cycle

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![Graphs showing changes in LVEF, BNP, AHI, CAI, and OAI before and after treatment](image-url)
Medical Management of Heart Failure

**Medical therapy:**

- **ACE-Inhibitors:** *Br Heart J* 1995; 73: 237-241
  - Captopril 75 mg daily
    - N1, N2 sleep and arousals were reduced, along with apneic events
    - ↓ mortality by 18% with Enalapril; only 12% reduced NYHA class to I-II (*NEJM* 1987; 316: 1429-1435)

- **Diuretics:** restore euvolemia, reduce pulmonary congestion

- **Spironolactone**
  - NYHA II-IV with an EF 35% or less
  - ↓ mortality by 30%, but no change in NYHA class in 59% (*NEJM* 1999; 341: 709-717)

- **Non-pharmacologic therapies:**
  - Cardiac rehabilitation
  - Cardiac resynchronization therapy (CRT)
  - Atrial overdrive pacing (AOP): has been able to reduce AHI by 50%
  - Automatic internal cardiac defibrillator placement (AICD)
  - Left ventricular assist device placement (LVAD)
  - Heart transplantation
Cardiac Resynchronization Therapy

CRT

- 20+ years of use in patients with:  
  - Chronic heart failure (NYHA I-IV)  
  - Impaired LV function  
  - Wide QRS complex with QRS duration ≥ 120 ms

- Multiple clinical trials* have demonstrated:
  - Safety & efficacy  
  - Improved walk distance, exercise capacity & quality of life  
  - Oxygen uptake (VO2)  
  - Improved LVEF, reversed LV remodeling  
  - Reduced death and HF hospitalizations

- Additional benefit was seen by adding AICD:  
  - Improved survival, 20% reduction in death or hospitalization compared to pharmacological therapy alone (except in NYHA class IV)

- Non-responders: 33% of patients did not have improvement in NYHA class or EF with CRT

* MUSTIC, PATH-HF, MIRACLE, MIRACLE-ICD, COMPANION, CARE-HF, CONTAK CD, MIRACLE ICD II, MADIT-CRT, REVERSE, RAFT
Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT)

- Simultaneous pacing of 1 or both ventricles in those with bundle branch block and ventricular dyssynchrony
- Meta-analysis of 6 studies:
  - AHI decreased by 12 events per hour (range 6-15)
  - LVEF increased by 8 % (range 3.9-14 %)

SLEEP 2012; 35(1):17-40
CPAP Therapy

Several studies have shown CPAP:

- Reduces or eliminates CSA in patient with CHF
- Increases left ventricular ejection fraction
- Reduces plasma norepinephrine and atrial natriuretic peptide
- Improves quality of life

**CPAP:** (meta-analysis; n=168-191)
- AHI: ↓ 21 / h
- EF: ↑ 6 %
CANPAP Trial: NEJM 2005; 353:2025-33

CANPAP Trial:
- 258 patients, randomized to 10 cm water pressure CPAP (or highest tolerated pressure < 10 CWP) or control
  - Stable CHF (NYHA class II-IV), EF < 40%, on medical therapy x 1 month
  - CSA with AHI ≥ 15, with more than 50% due to central events

CPAP Results:
- Reduced AHI by 21 events per hour, compared to 2 in control group
- Increased O2 saturations
- No change in sleep or arousals
- EF improved by 2.2%
- Reduced norepinephrine
- Death rate, number of hospitalizations, quality of life and rate of heart transplantation were the same between the CPAP and control groups
**CANPAP Trial:** *NEJM 2005; 353:2025-33*

<table>
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<th>Cause</th>
<th>Control Group</th>
<th>CPAP Group</th>
<th>no. (%)</th>
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<td>Cardiovascular</td>
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<td>Progressive heart failure</td>
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<td>Sudden death</td>
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<td>9 (33)</td>
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<td>Total</td>
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<td>27</td>
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* Cardiovascular causes accounted for 78 percent of the deaths. There were no significant differences in the causes of death between the control group and the CPAP group or in cardiovascular causes of death (73 percent vs. 85 percent in the control group and the CPAP group, respectively; \(P=0.33\)).

**Figure 3. Heart-Transplantation-free Survival.**

There was no difference in transplantation-free survival rates between the control group and the CPAP group (hazard ratio for transplantation-free survival, 1.16; \(P=0.54\)). However, there was an early divergence in the event rates that favored the control group (hazard ratio for transplantation-free survival, 1.5; \(P=0.02\)) that altered after 18 months to favor the CPAP group (hazard ratio for transplantation-free survival, 0.66; \(P=0.06\)).
Post-Hoc Analysis of CANPAP Trial

**CPAP Therapy:**

- Re-examination of the CPAP treatment arm, separating it into those who responded to CPAP with AHI < 15 and those that did not
  - 43% were non-responders
  - Non-responders tended to have higher AHIs and more central events at baseline prior to CPAP

*Circulation 2007; 115:3173-3180*
Post-Hoc CANPAP Trial

AHI Results:
- Control – 36
- CPAP Non-responders – 35
- CPAP Responders – 6

LVEF Change:
- Control – 0.3%
- CPAP Non-responders – 0.4%
- CPAP Responders – 3.6%

Mortality & Transplant Events:
- Control – 23% events
- CPAP Non-responders – 30%
- CPAP Responders – 9% events

CPAP: (n=100)
- Responders: 57%
  - AHI: ↓ 30 / h
  - EF: ↑ 3.3%
Bilevel ST Therapy

Bilevel ST:
Treatment of CPAP non-responders with Bilevel ST therapy:

- 20 patients: CHF (NYHA II-III) and CSA-CSR with AHI \( \geq 15 \)/h, over 50% of events being CSA/H
- First treated with CPAP with average pressure of 9.1 CWP (range 8-10)
- Divided into CPAP responders if AHI < 15, or non-responders if AHI \( \geq 15 \)
  - CPAP responders continued CPAP (n=11)
  - Non-responders had Bilevel ST titrated: IPAP 11.7±1.3, EPAP 6.2±0.4 with preset RR
  - Non-responders had lower pCO\(_2\) levels, higher plasma BNP, longer CSR cycle times, lower levels of OSA

*Circ J 2008;72:1100-5*
Supplemental Oxygen

- Several studies demonstrated that O$_2$: *SLEEP 2012; 35(1):17-40*
  - Reduces or eliminates CSA
  - Increases LVEF
  - Reduces arousals, improves exercise tolerance, quality of life and cognition
  - Reduces sympathetic nervous activity and BNP levels
  - Does NOT change ventricular arrhythmias;
  - No benefit on transplant free survival
  - There were responders with AHI < 15 and non-responders; non-responders had lower pCO$_2$ levels (36.1 vs. 39.3 in responders). *SLEEP 1999;22:1101-6*

- Proposed mechanism:
  - Hyperoxia reduces peripheral CO$_2$ chemosensitivity, thus reducing controller gain
  - O$_2$ may increase cerebral CO$_2$ levels

**O$_2$: (meta-analysis; n=42-49)**
- AHI: ↓ 15 / h
- EF: ↑ 5 %
Supplemental Oxygen

- 52 patients followed for 1 year and randomized to O2 or none
  - Stable HF (NYHA II-II) with hospitalization with 1 year
  - LVEF ≤ 45%
  - AHI ≥ 5 with over 50% due to central apneas
  - 26 were treated with 3 L/min oxygen x at least 4 hours per night

- Results for O2 treated group
  - AHI was reduced from 19 to 8.4 due to reductions in CAI and HI; OSA was not changed
  - pCO2 increased from 37.1 to 39.5
  - NYHA improved in 41.7%
  - EF improved from 33% to 38.5%
  - No change in NE, BNP or ANP
  - No change in the combined end-point of cardiac death, hospitalization for HF and worsening Specific Activity Scale
  - Cardiac events 38% in treatment group (vs 40% in control group)

*Circ J 2009; 73: 1255-1262*
Case Presentation:

**Summer 2015:**

Clinic follow-up: OSA and CSA/CSR

- The patient’s sleep has not been as good off ASV; still waking up gasping for air. Could not tolerate trial of CPAP

- 1 month after biventricular pacemaker with AICD placement, a split-night sleep study was repeated on Ambien CR 6.25 mg with plan to retitrate CPAP for obstructive events + add O2 or try Bilevel ST for on-going central events

Split-night polysomnography ordered to see if central apneas would persist with better ventricular synchrony

Instructions to tech: 1) Score all hypopneas as central or obstructive

2) If AHI ≥ 5 due with obstructive events, titrate CPAP

3) If CAHI > 50% of events, add O2 to CPAP or switch to Bilevel ST
Split-Night Polysomnography Results

**BASELINE:**

TRT: 2.3 hours, TST: 1.3 hours, SE: 57%
N1 41%, N2 59%, N3 & REM 0%

**AHI: 59.2**
- OSA: 35
- CSA: 23 (Cheyne-stokes was present)
- Mixed apneas: 8
- Obstruction hypopneas: 11 due to mild snoring
- Central hypopneas: 0

Lowest O2 saturation: 91%
PLMI 0, PLMAI 0

**TITRATION:**

**CPAP Titration:** (CPAP 4 to 10 cm water pressure)
TST: 2.9 hours, SE: 55%

**AHI: 32.4**
- OSA: 6; Mixed: 13; OH: 6
- CSA: 57 (Cheyne-stokes was present); CH: 12
Lowest O2 saturation: 88%

**CPAP + O2:** (CPAP 10 CWP + 3 L/min oxygen)
TST: 0.6 hours, SE: 55%

**AHI: 31.7**
- OSA: 0; Mixed: 0; OH: 0
- CSA: 16 (Cheyne-stokes was present); CH: 3
Lowest O2 saturation: 89%

OSAI: 41.5
CSAI: 17.7

OSAI: 8.6
CSAI: 23.8

OSAI: 0
CSAI: 31.7
Case Presentation

Summer 2015

Clinic follow-up for sleep study

- Patient continues to have significant sleep disordered breathing, including CSA-CSR despite:
  - Medical optimization with medications, euvolemia, and CRT, AOP and AICD placement
  - Ambien had no effect on sleep parameters
  - Non-responder to CPAP (felt worse with trial of CPAP 8 cm water pressure), Non-responder to O₂ at 3 L/min

- Discussion regarding other possible treatment options:
  - Re-titrate with Bilevel ST therapy
  - Trial of acetazolamide

- Patient wished to restart ASV therapy despite the cardiovascular risk; he felt best on this therapy and wanted to restart this despite risks to improve his quality of life/sleep
  - He decided not to have colostomy reversed and has been sleeping better since making this decision
  - Ambien D/C’d. ASV restarted.
Acetazolamide (Diamox)

- **Mechanism**
  - Respiratory stimulant: induces hyperventilation and increased oxygen intake, this is how it counteracts the periodic breathing of altitude sickness
  - Carbonic anhydrase inhibitor that leads to the excretion of $\text{HCO}_3^-$ from the kidneys, thus causing a metabolic acidosis that lowers the AT and increases the PCO2 reserve
  - Mild diuretic

- **Acetazolamide 3.5 - 4 mg/kg daily to decrease $\text{CO}_2$ by 5 mmol (+ KCl 30 meq daily)** *AJRCCM 2006; 173:234-7*
  - 12 patients with CHF (NYHA II-III), LVEF ≤ 35
  - CSR with AHI > 15/h
  - Reduced AHI with subjective improvement in daytime and sleep symptoms
  - 1 patient developed significant dyspnea with the medication; no other major side effects were reported; pCO$_2$ dropped by 2.8 mmHg

- **Treats primary CSA (idiopathic) and CSA due to high altitude**

<table>
<thead>
<tr>
<th>Pco$_2$, mm Hg</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Acetazolamide</th>
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<tbody>
<tr>
<td>Pco$_2$, mm Hg</td>
<td>37.0 ± 2.7</td>
<td>35.2 ± 2.7</td>
<td>34.2 ± 2.7</td>
<td>0.003</td>
</tr>
<tr>
<td>[HCO$_3^-$], mmol/L</td>
<td>36.6 ± 2.0 (pH 7.44)</td>
<td>37.1 ± 2.9 (pH 7.43)</td>
<td>43.5 ± 4.0* (pH 7.36)</td>
<td>0.001</td>
</tr>
<tr>
<td>[Na$^+$], mmol/L</td>
<td>139 ± 2</td>
<td>140 ± 3</td>
<td>139 ± 3</td>
<td>0.2</td>
</tr>
<tr>
<td>[K$^+$], mmol/L</td>
<td>4.2 ± 0.4</td>
<td>4.3 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>[Cl$^-$], mmol/L</td>
<td>103 ± 5</td>
<td>103 ± 2</td>
<td>106 ± 5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AHI, no./h</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Acetazolamide</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 ± 24</td>
<td>49 ± 28</td>
<td>34 ± 20*</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>44 ± 23</td>
<td>49 ± 28</td>
<td>23 ± 21*</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>1 ± 2</td>
<td>2 ± 5</td>
<td>2 ± 5</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>10 ± 10</td>
<td>8 ± 6</td>
<td>12 ± 8</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>30 ± 25</td>
<td>22 ± 18</td>
<td>17 ± 6</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>25 ± 18</td>
<td>20 ± 19</td>
<td>13 ± 6</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline Sa$_{O2}$ %**
- 96 ± 2

**Lowest Sa$_{O2}$ REM %**
- 86 ± 6

**Lowest Sa$_{O2}$ NREM %**
- 84 ± 5

**Sa$_{O2}$ % 90%, % TST**
- 16 ± 19

Acetazolamide: (n=12)
- AHI: ↓ 21 / h
- EF: 6
Transvenous Phrenic Nerve Stimulation

Unilateral PNS Therapy

• Requires transthoracic surgical placement of:
  • An implantable pulse generator
  • Stimulation leads placed in right or left brachiocephalic vein or left pericardiophrenic vein to stimulate the phrenic nerve

• Device delivers currents up to 7-10 mA to stimulate breathing and promote a more normal breathing pattern

• Unilateral current results in bilateral diaphragm contraction

• Similar therapy is used for high cervical spinal cord injury and congenital central hypoventilation syndrome (Ondine’s curse)
Transvenous Phrenic Nerve Stimulation

**Unilateral PNS Therapy:** Short Term Study

- 16 patient followed pre & post 1 night placement of a PNS unit:
  - Stable CHF with LVEF ≤ 45%
  - AHI ≥ 15 /h, CAI ≥ 5
  - Excluded phrenic nerve palsy, coagulopathy, pacemaker dependent, hypoxia
- PNS stabilizes CO₂ levels, improves oxygenation and promotes a more normal breathing pattern; most stabilized with 3.5-5.3 mA
  - AHI was reduced by 22/hr
  - 31% had reduction in AHI < 15
- Adverse effects reported:
  - Lead thrombus
  - Ventricular tachycardia
- At 10 mA, there was no detection of PNS by ICDs or CRT-ICDs

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*Eur Heart J* 2012; 33: 889-894

**PNS: (n=16)**
- Responders: 31%
  - AHI: ↓ 22 / h
  - EF: ?
Phrenic Nerve Stimulation

**Unilateral PNS Therapy:** 6 Month Study

- 47 patients followed for 6 months after placement of a PNS unit:
  - Stable CHF with LVEF ≤ 45%
  - AHI ≥ 15 /h, CAI ≥ 5
  - Excluded phrenic nerve palsy, coagulopathy, pacemaker dependent, hypoxia

- Results of PNS placement
  - Improved sleep efficiency, more REM sleep, reduced arousals
  - Improved oxygenation
  - AHI was reduced by 24 with reductions in CAI, OAI, MAI and HI

- Adverse effects reported:
  - 1 death from heart failure (2%)
  - Hematoma
  - Migraine
  - Atypical chest pain

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 Months</th>
<th>6 Months</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, episodes/h of sleep</td>
<td>49.4 ± 14.9</td>
<td>22.8 ± 13.6</td>
<td>23.3 ± 13.3</td>
<td>≤0.0001*</td>
</tr>
<tr>
<td>CAI, episodes/hr of sleep</td>
<td>28.1 ± 14.7</td>
<td>5.0 ± 8.8</td>
<td>4.5 ± 7.2</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>OAI, episodes/hr of sleep</td>
<td>3.0 ± 2.8</td>
<td>3.9 ± 4.8</td>
<td>3.8 ± 5.2</td>
<td>0.0223†</td>
</tr>
<tr>
<td>MAI, episodes/h of sleep</td>
<td>3.0 ± 3.7</td>
<td>0.3 ± 0.6</td>
<td>0.6 ± 1.5</td>
<td>&lt;0.0002*</td>
</tr>
<tr>
<td>HI, episodes/h of sleep</td>
<td>15.4 ± 12.4</td>
<td>13.5 ± 9.0</td>
<td>14.4 ± 8.3</td>
<td>0.0179†</td>
</tr>
<tr>
<td>ODI4, episodes/hr of sleep</td>
<td>46.0 ± 18.8</td>
<td>22.0 ± 13.8</td>
<td>22.9 ± 13.3</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Arousal index, episodes/h of sleep</td>
<td>35.5 ± 18.4</td>
<td>23.4 ± 10.9</td>
<td>24.7 ± 12.3</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>69.3 ± 16.8</td>
<td>76.9 ± 15.6</td>
<td>81.4 ± 12.5</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>REM sleep, %</td>
<td>11.2 ± 6.3</td>
<td>16.2 ± 8.1</td>
<td>17.4 ± 6.9</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>
Advanced Titration Strategy in Chronic Heart Failure

Sleep Medicine Consult for CHF, arrhythmia & significant cardiovascular disease & symptomatic from SDB

**Optimize Medical Management of Heart Failure**
- Euvolemia, B-blocker, ACE-I, spironolactone
- Candidate for CRT/AICD

**Polysomnography**
- Predominantly CSA
- Predominantly OSA

**EF ≤ 45%**
- Echocardiogram

**EF > 45%**
- Polysomnography

**Predominantly CSA**
- Echocardiogram
- CPAP Titration
  - AHI ≥ 15
    - Bilevel ST Titration
      - Responder: AHI < 15
        - Treat with Bilevel ST
      - AHI ≥ 15
        - Treat with CPAP
    - Responder: AHI < 15
      - Treat with ASV
      - ASV Titration
      - If CSA develops & predominates

**Predominantly OSA**
- Follow OSA Titration Protocols
  - CPAP Titration
    - AHI ≥ 15
      - Bilevel ST Titration
        - Responder: AHI < 15
          - Treat with Bilevel ST
        - AHI ≥ 15
          - Treat with CPAP

**Non-responsive or Intolerant to PAP Therapy**
- Consider Additional Treatment Options
  - Supplemental oxygen
  - Acetazolamide, Peripheral Nerve Stimulation
  - Intensify medical management, if possible

- ASV Titration
  - Responder: AHI < 15
    - Treat with ASV
    - If CSA develops & predominates
Summary

• CHF patients have complicated sleep disordered breathing that is a mixture of obstructive, central and mixed events

• CHF carries a stubbornly high morbidity and mortality despite advances in pharmacological and interventional therapies; optimizing and tailoring therapy to the patient is critical

• Patients may respond or not-respond to therapy; careful long-term follow-up is needed as well as good communication with cardiology
  • It may takes weeks to months after an intervention to improve high loop gain
  • Some interventions may make central sleep apnea better, but worsen obstructive events
Month Of Publication: Summer 2017

– 3 years later

Interval History:
- Doing better than he has in years; staying active teaching others about AICD & colostomy and chasing after his grandchildren. NYHA 1.
- Has energy during the day, no sleep disruption
- Echocardiogram 6/7/2016: EF 35-40%; dysynergistic septal motion (compared to 5/13/2015) has now subsided
- Echocardiogram 3/3/2017: Normal LV size. Akinetic LV apical anterior and septal segments. LVEF 50%. Grade 2 DD. Mild LAE. Mild MR. RVSP 29 mmHg.

Download information: 6/26/2017 – 8/8/2017
- ASV was used 44 out of 44 days and for 4 or more hours 100% of the time
- Average daily use is 7 hours, 52 minutes
- No large leak; residual AHI: 0.5