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Treatment of Central and Complex Sleep Apnea

Nancy Collop, MD
Emory University

Conflicts of Interest

- Royalties from UPTODATE as an author and editor
- Received grant monies and was on advisory council for Jazz Pharmaceuticals (2017-2018)

Central Sleep Apnea

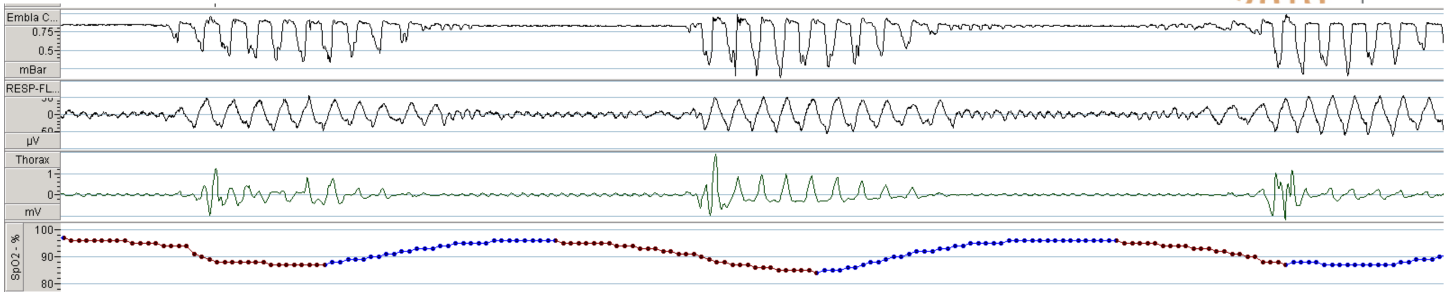
Common etiologies:

- Heart failure
- Stroke
- Opioid use
- PAP Emergent
- Idiopathic

Central Sleep Apnea

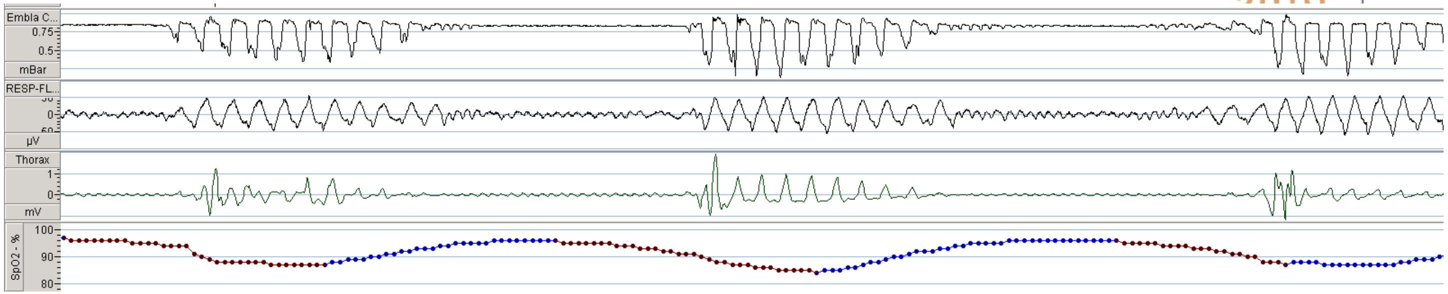
A diagnosis of **central sleep apnea (CSA)** requires all of the following:

– An apnea hypopnea index > 5
– Central apneas/hypopneas > 50% of the total apneas/hypopneas
– Central apneas or hypopneas ≥ 5 times per hour
– Symptoms of either excessive sleepiness or disrupted sleep



How should this be scored?

1. Obstructive sleep apnea
2. Biot’s breathing pattern
3. Central hypopneas
4. Obstructive hypopneas
5. Cheyne Stokes breathing pattern



How should this be scored?

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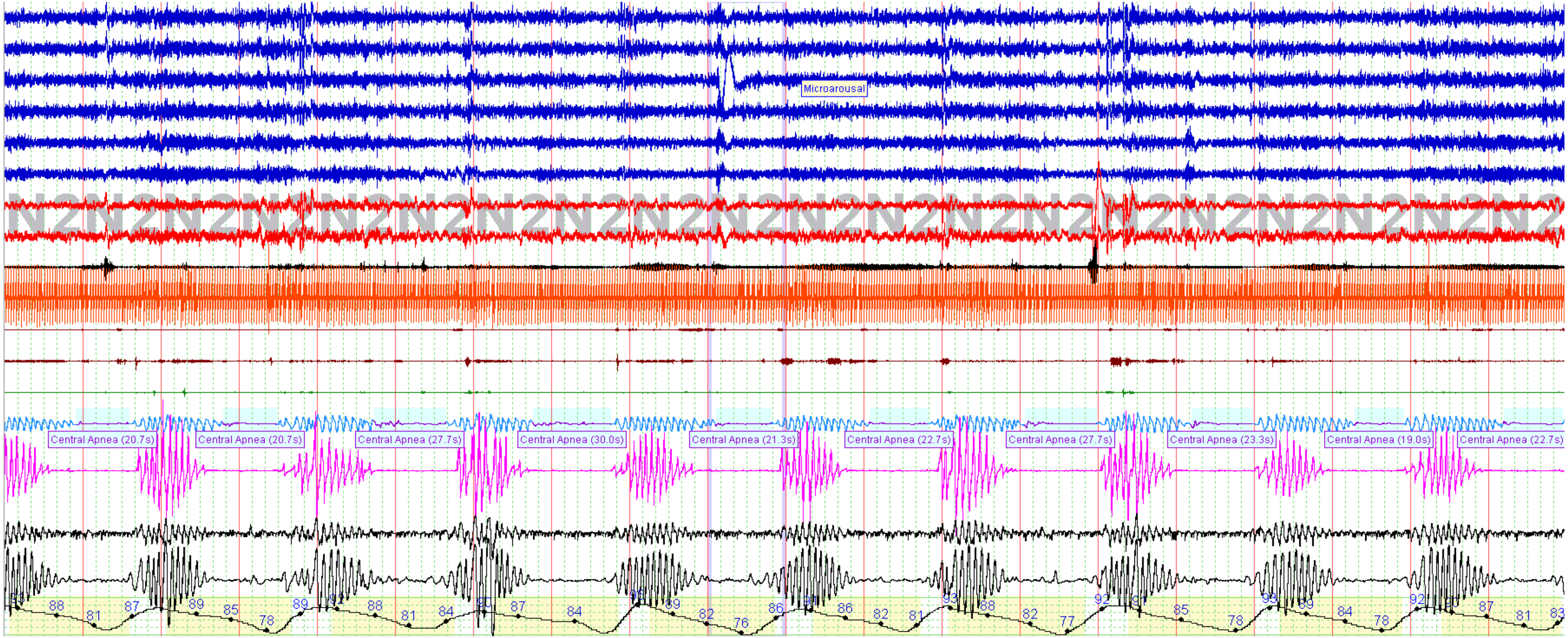
3. Central hypopneas
4. Obstructive hypopneas
5. <u>Cheyne Stokes breathing pattern</u>

CSA/CSR in CHF

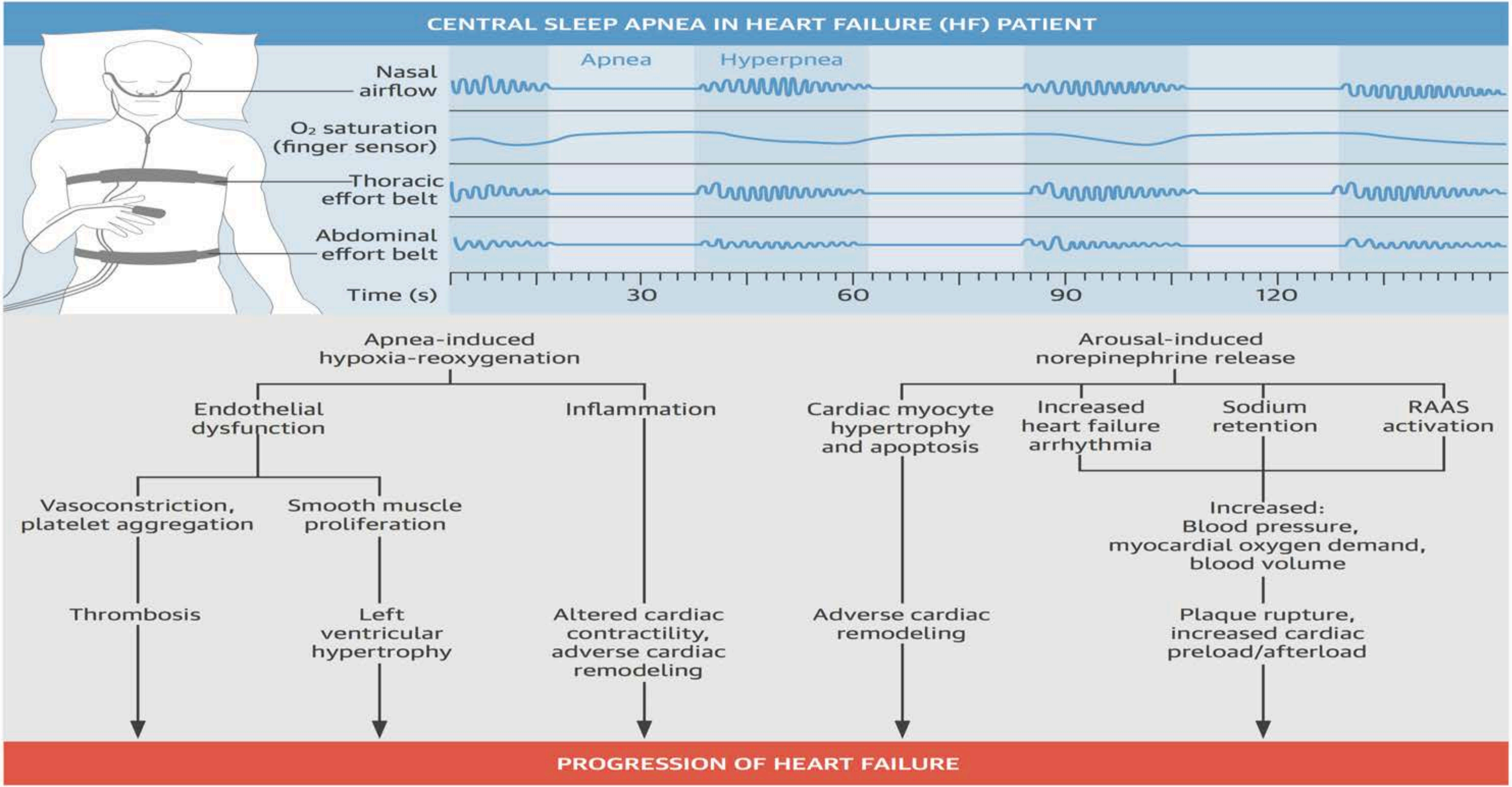


Cheyne Stokes Breathing and CHF

- CSB is relatively common (33%) in patients with CHF
- Rule of Thirds: 1/3 CSA, 1/3 OSA and 1/3 neither
- Associated with increased morbidity and mortality in patient with CHF
- May lead to sleep fragmentation and daytime sleepiness

Risk factors:

- Male
- Age > 60
- Higher NYHA class
- Hypocapnia during wakefulness (< 38 mm Hg)
- Atrial fibrillation
- Higher BNP levels



Costanzo et al, J Am Coll Cardiol 2015; 65(1):72-84

Clinical Consequences of Central Sleep Apnea

Initial Cheyne Stokes Management in CHF

↓

Maximize Medical Therapy

Other Treatments for CSB in CHF

- **PAP**
  - CPAP may work for some
  - ASV
- **Oxygen**
  - May decrease AHI and improve SpO_2
  - No long term data
- **Transplant**
  - Improves CSR, but may be delayed
- **Phrenic nerve stimulator**
  - Inserted transvenously

Recommendations for tx of sleep-disordered breathing in CHF

- If OSA predominant, CPAP is the mainstay of therapy
  - If CSA persists or emerges (>5/hr) with OSA controlled, ASV trial recommended
- If CSA predominant, CPAP trial to see if AHI<15 can be achieved
  - If not, ASV trial recommended (if EF>45%)
  - Otherwise, optimize heart failure, may consider CPAP plus oxygen or bilevel PAP with BUR
  - ? Phrenic nerve pacing
  - Avoid autotitrating devices

TREATMENT EMERGENT CSA (TECSA)

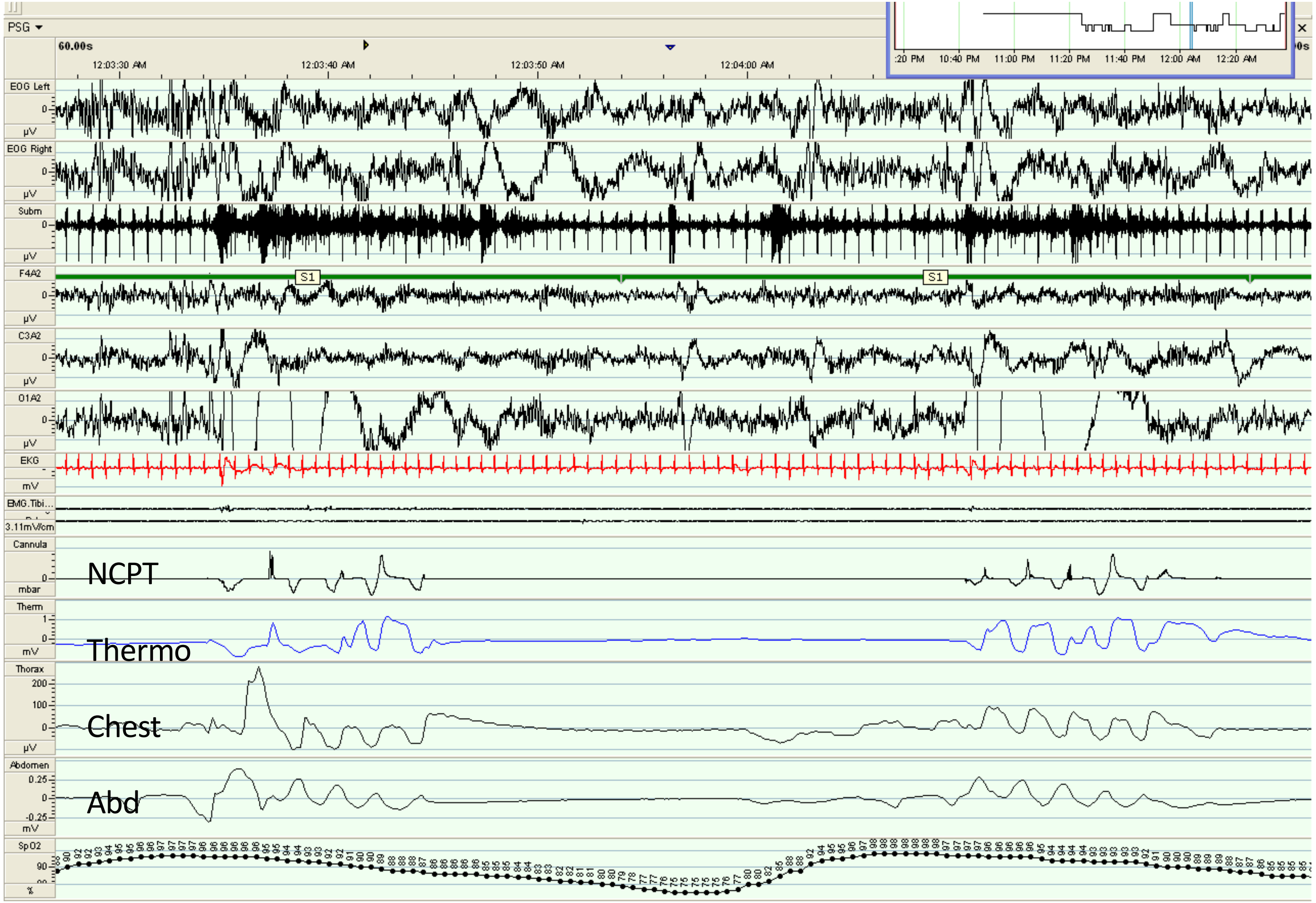
aka Complex Sleep Apnea

Treatment Emergent CSA (TECSA)

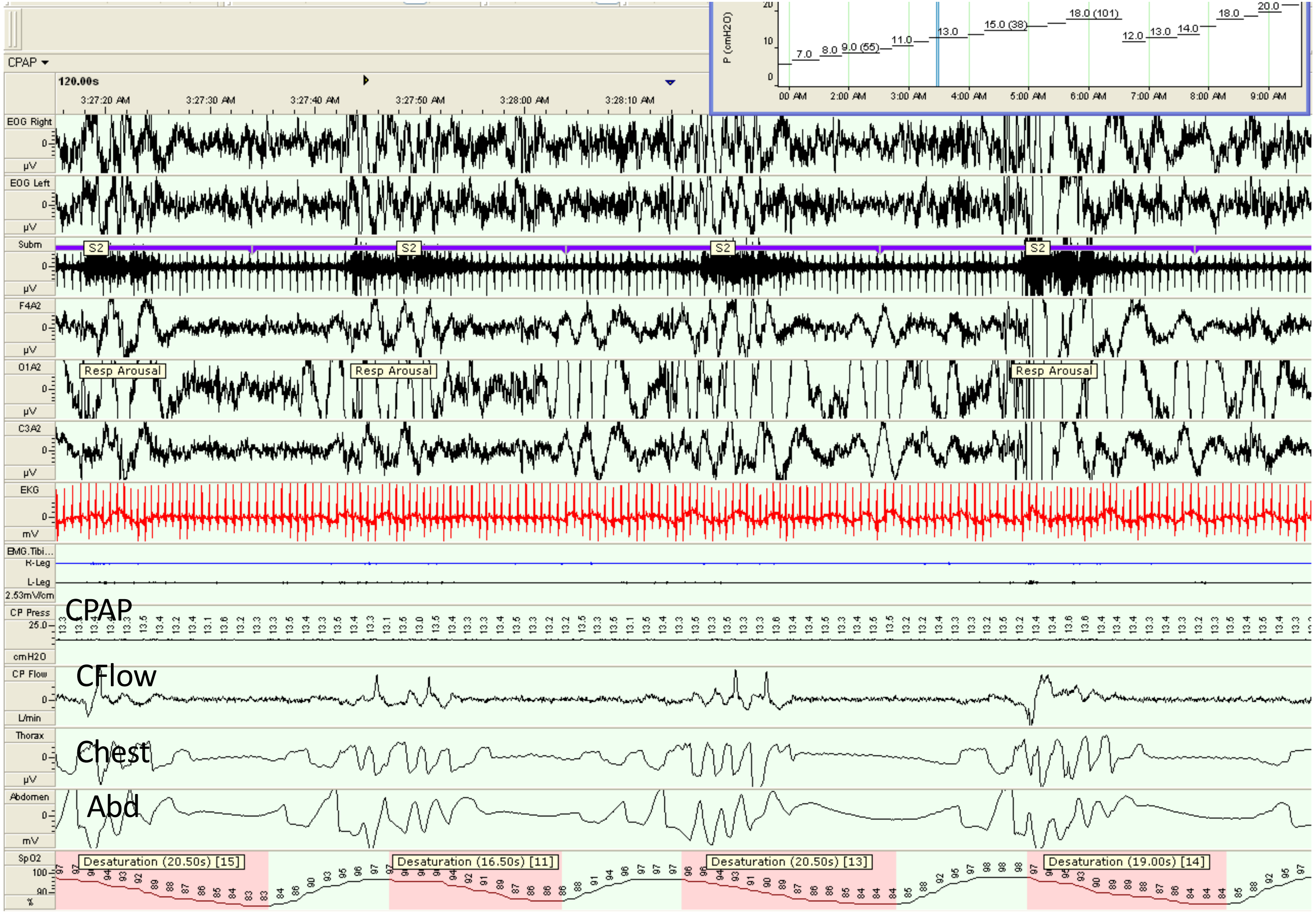
- Predominantly obstructive events on a diagnostic study with persistence or emergence of central events during PAP therapy
- Central events not better explained by another disorder
- Reported prevalence 2%-20%
- Significance and long term outcomes unknown

American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien IL: American Academy of Sleep Medicine, 2014

Baseline: has recurrent events as seen here



CPAP: continues to have similar events at all pressures



Treatment-emergent Sleep Apnea

- Development of CSA during therapy for OSA
  - Unmasking previously-existing CSA
  - Overtitration of CPAP
    - Hering-Breuer reflex
  - More effective ventilation with relief of obstruction
- Can occur with other forms of therapy as well!
  - OAT, UA surgery, tongue retaining device

Hoffman and Schulman, Chest 2012; 142(2): 517-22.

Therapy Options

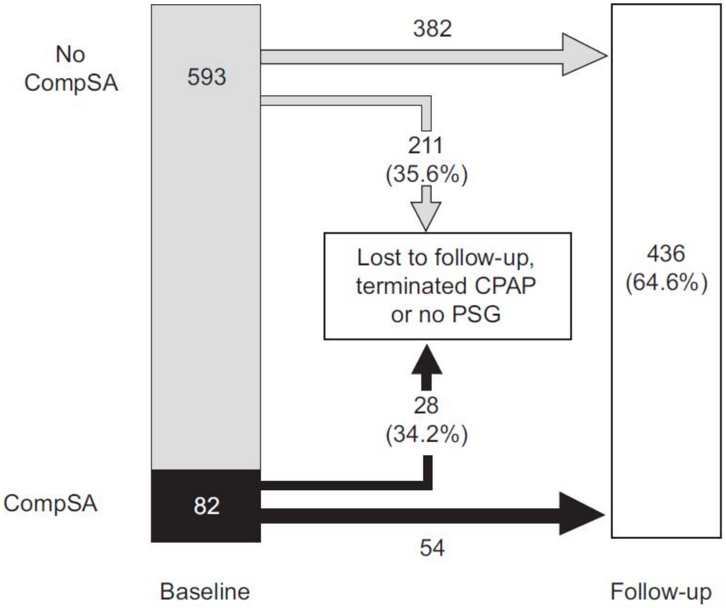
- Determine if there is a potential etiology for centrals
- If specific etiology found, may target that initially
- Consider drug trial
  - Reduce arousals
  - low level evidence
- PAP therapy
  - Best CPAP and re-evaluate; monitor leak
  - ASV

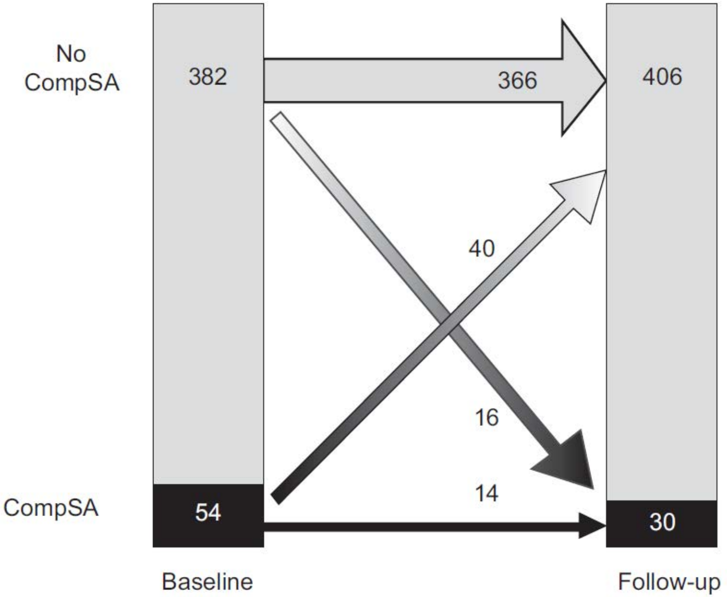
TECSA may go away or start with CPAP therapy

- Prospective study
- Utilized full PSG (no split nights, no HST)
- 675 pts
- Polysomnography
  - Baseline
  - On therapeutic CPAP
  - 3 months after CPAP therapy

Eur Respir J 2011;38:329-37

TECSA may go away or start with CPAP therapy





Eur Respir J 2011;38:329-37

Natural History of TECSA

- Analysis of US telemonitoring device data at week 1 and week 13 after CPAP initiation (133,006 pts)
  - 3.5% of patients with CSA (≥ 5/h)
  - Of those: 55% were transient, 25% persistent and 19.7% emergent
  - More leaks
- Similar results seen in systematic review of literature: (5 studies):
  - 1/3 of patients with TECSA have persistence of TECSA (TPCSA)
    - Have higher CAI
    - May have lower adherence
  - Up to 4% of patients with0ot TECSA can develop delayed TECSA (D-TESCA)

Chest 2017;152(4):751-760
Ann Thorac Med 2018;13(2):86-91

OPIOID INDUCED CSA

Ataxic Breathing Pattern (Biot's)

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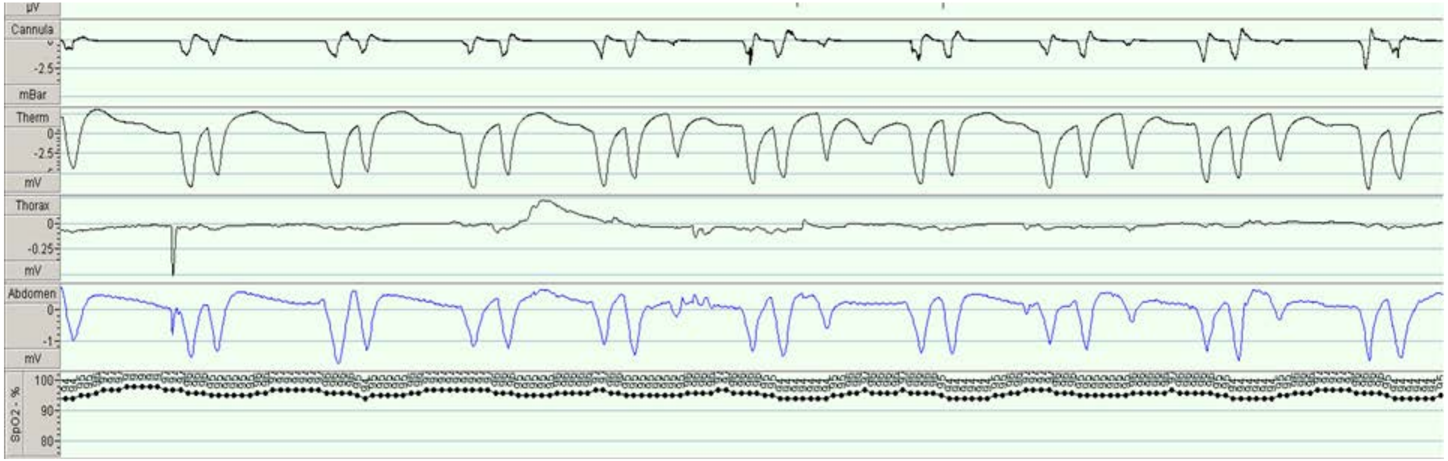
- Methadone
- Oxycontin
- Fentanyl patch
- Suboxone



Opioid Related Sleep Disordered Breathing

- Opioid related sleep disordered breathing:
  - Central apneas including Biot's pattern
  - Prolonged obstructive hypoventilation
  - Obstructive apneas and hypopneas
  - Mixed pattern of sleep disordered breathing
- Most commonly associated with long acting opioids
- Dose dependent relationship with narcotics
- Typically does <u>not</u> resolve spontaneously
- Optimal treatment <u>not</u> clear
  - May respond best to a reduction in dose of opioids
  - ASV treatment data <u>used but not as effective as in CSB</u>

ADAPTIVE SERVOVENTILATION

Adaptive Servoventilation (ASV)

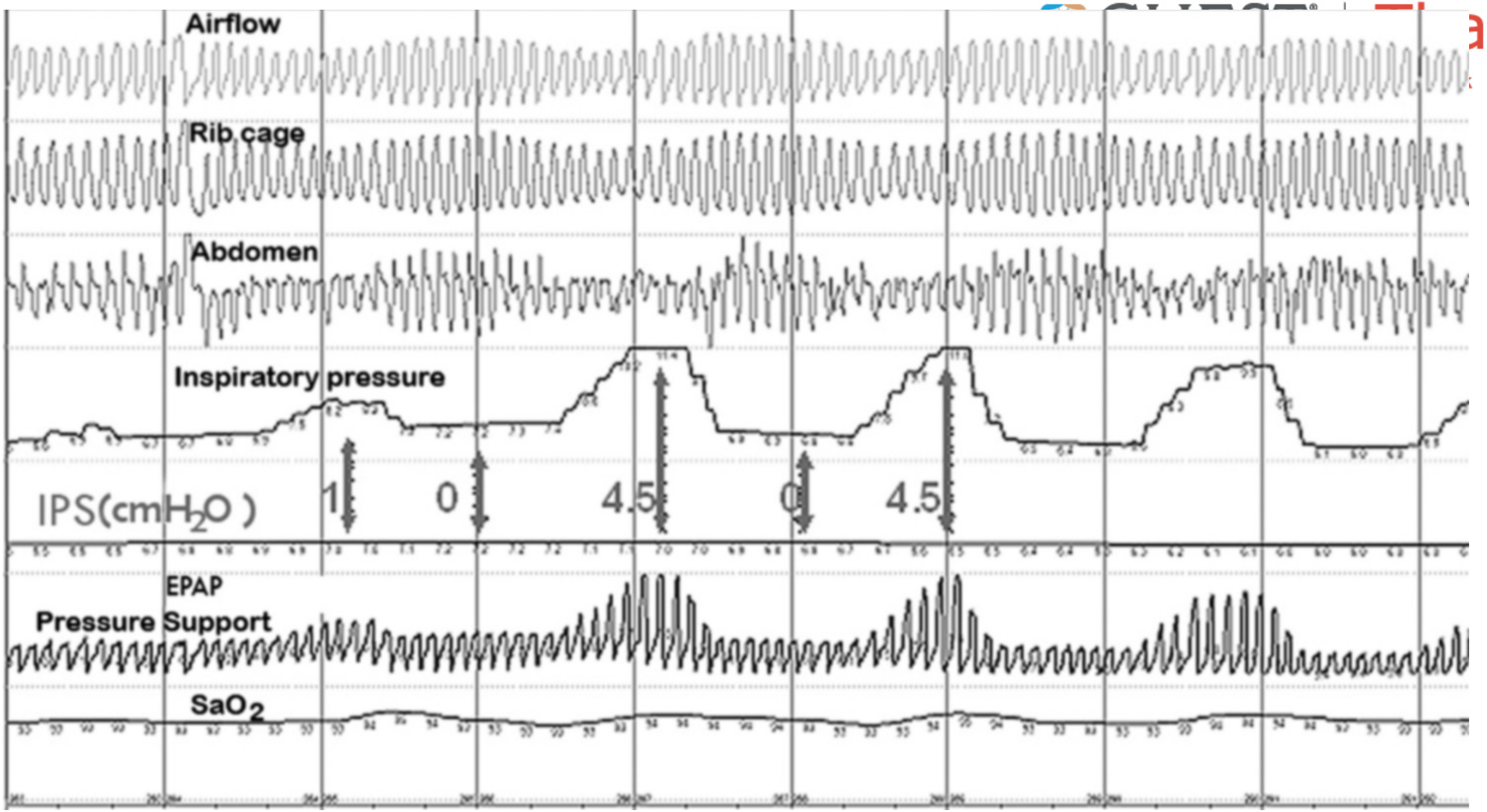
- Non-invasive automated Bilevel Positive Airway Pressure Device
- Aims to stabilize respiratory drive by varying amount of pressure support
- Also called anticyclical ventilation (to patient’s own respiratory drive)

ASV: how does it work?

- Continuously tracks patient's airflow (3-4 minute window)
- Calculates average weighted minute ventilation (Resmed) or peak flow (Respironics)
- Device adjusts respiratory parameters to maintain 90% of calculated MV or peak flow

ASV: how does it work?

- EPAP, set or auto-titrating: maintains upper airway patency
- Variable pressure support (PS min, PS max): targets 90%-95% of minute ventilation/peak flow to stabilize ventilatory drive
- Back-up rate: kicks in during central sleep apnea (CSA) events to maintain ventilation and stabilize drive



CHEST 2014; 146 (2): 514 - 523

ASV devices in the US

- ResMed Ltd:
  - Variable Positive Airway Pressure [VPAP] Adapt,
  - Aircurve 10 ASV
- Phillips Respironics:
  - BiPAP autoSV Advanced
  - Dreamstation BiPAP auto SV
- Description of algorithms : Javaheri, Brown, Randerath. CHEST 2014; 146 (2): 514 - 523

What is the major difference between Resmed and Respironics ASV algorithms?

A. Target minute ventilation vs peak flow
B. Min EPAP pressure
C. Ability to provide “auto” rate
D. Min Pressure support level

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Comparing Device Settings

	Aircurve 10 ASV (Resmed)	Dreamstation BiPAP auto SV (Respironics)
Target parameter	Average weighted MV (3 min)	Average weighted peak insp. flow (4 min)
Threshold	90% MV	95% peak flow
Max Pressure	25 cm of water	30 cm of water
Min/Max EPAP range	4-15 cm of water	4-25 cm of water
Min PS	0-6 cm of water	0-5 cm of water
Max PS	5-20 cm of water	0-26 cm of water
RR	Auto (15 bpm)	Off, auto or range 4-30 bpm
Apnea	MV drop ≥75% for≥10s	Flow drop ≥80%
Hypopnea	MV drop ≥50% for ≥10s	Flow drop ≥40%
Rise time	Automatic	Levels 0-3

CHEST 2014; 146 (2): 514 - 523

Indications

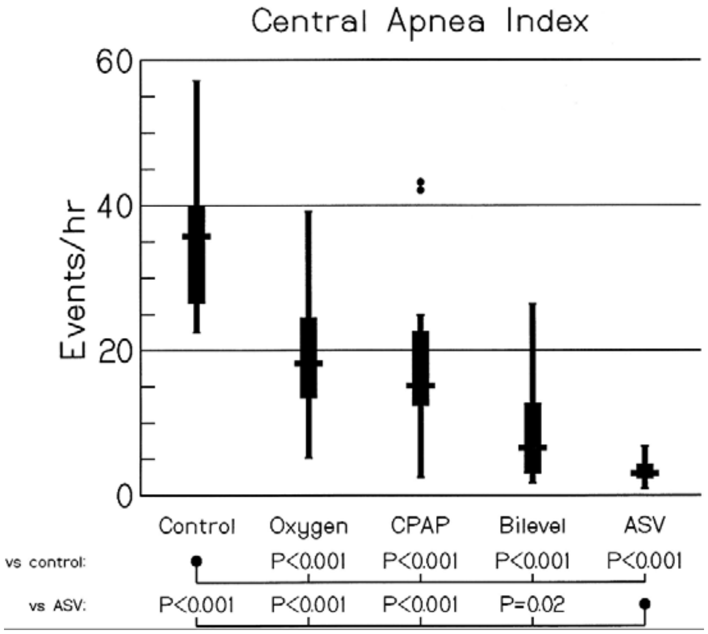
- Hypocapnic or eucapnic CSA
  - Treatment emergent CSA (TECSA)
  - CSA in Heart Failure with preserved Ejection Fraction (HFpEF)
  - Opioid related CSA (O-CSA)

Contraindications

- Predominant CSA in Heart Failure with reduced EF < 45%
- Hypoventilation (OHS, NM disease, Restrictive lung dz, chest wall deformities, moderate-severe COPD)

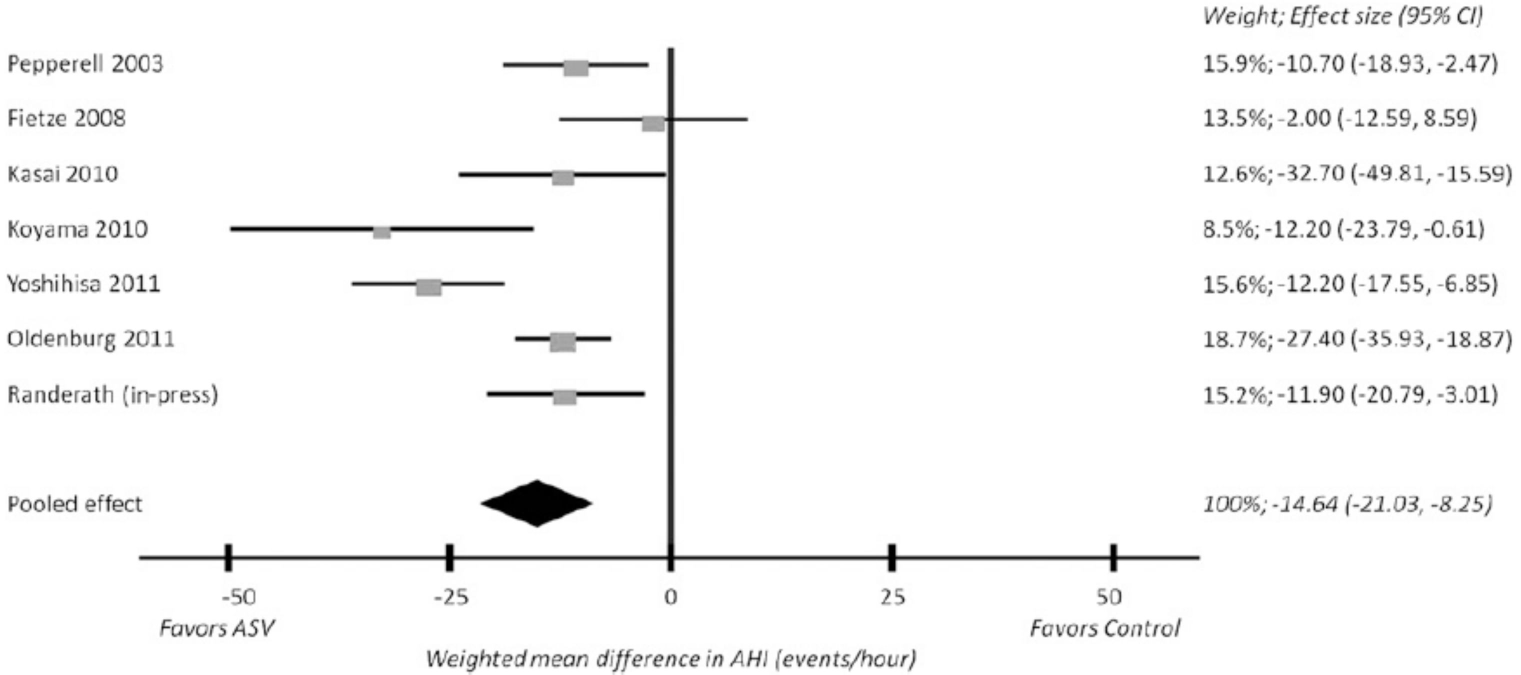
CSA/CSR in CHF

- Initial report of ASV efficacy in 2001
  - 14 subject with chronic heart failure (NYHA III)
  - Predominant CSA on PSG
  - 4 treatment nights



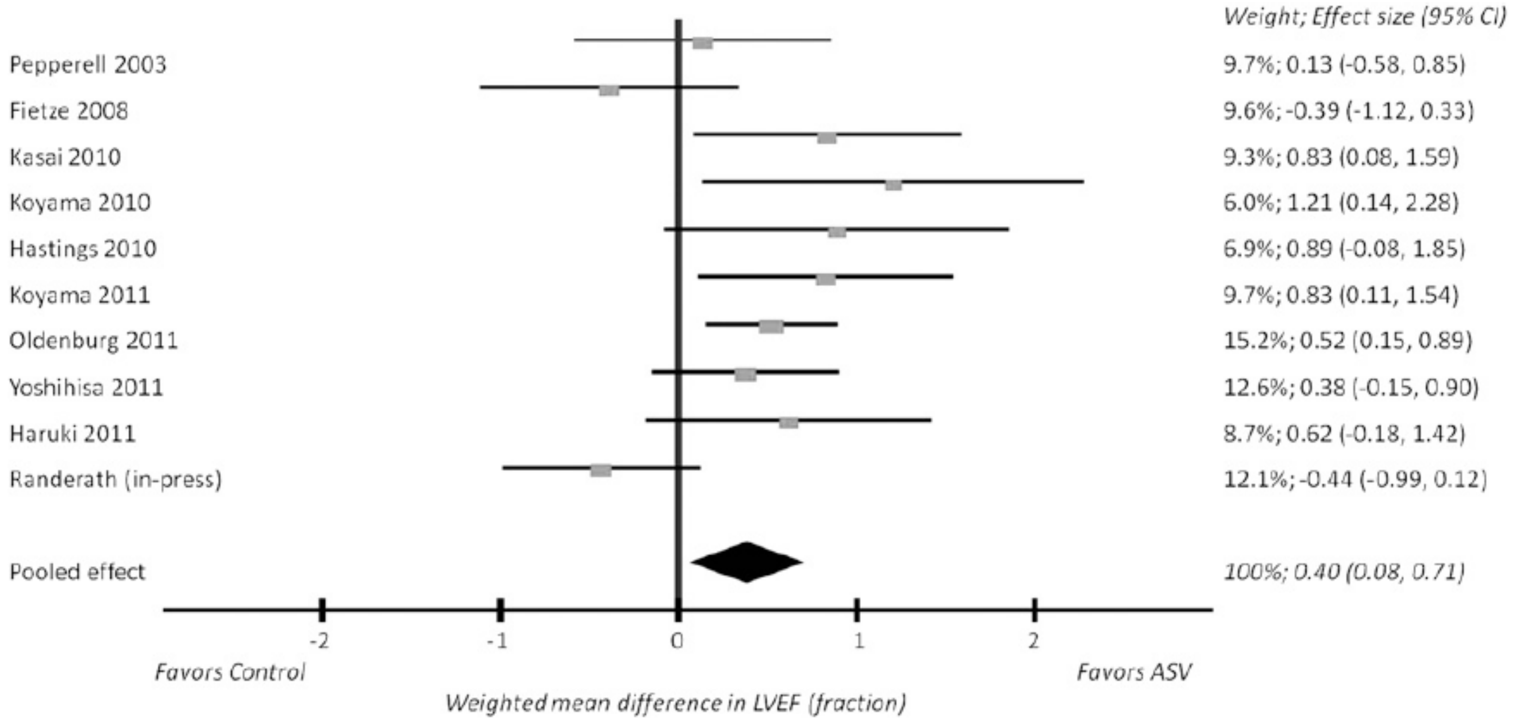
AJRCCM 2001;164(4):614-9

Effect of ASV on AHI in CHF



CHEST 2012; 142(5):1211–1221

Effect of ASV on LVEF in CHF



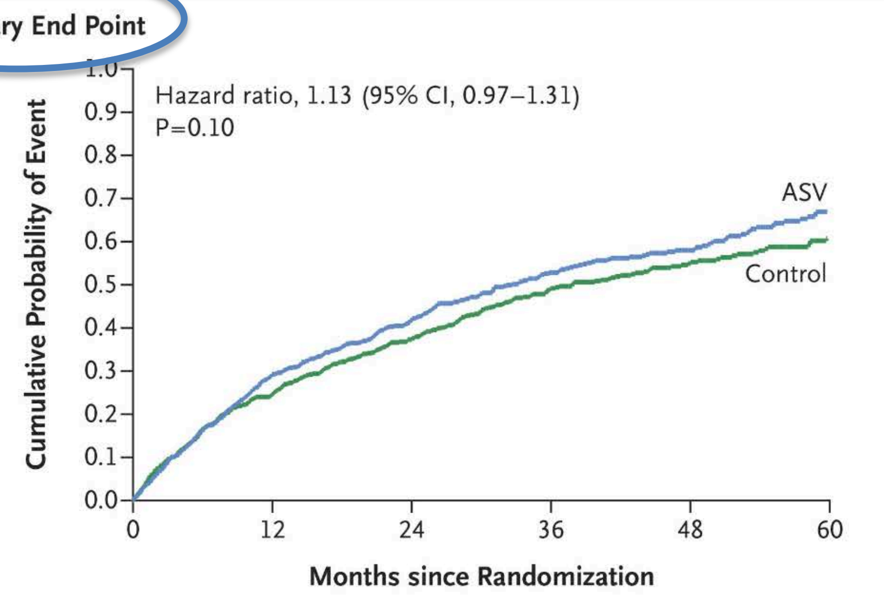
CHEST 2012; 142(5):1211–1221

SERVE-HF

- Design: International, multicenter, randomized, parallel group, event driven study
- Patients: 1325 patient, LVEF ≤ 45% and NYHA III or IV, or II with one hospitalization for HF in past 24 months; AND predominantly central sleep apnea with AHI ≥ 15
- Intervention: Randomized to medical management + ASV vs medical management alone (control)
- Primary end point = death from any cause, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening HF

N Engl J Med 2015; 373:1095-1105

SERVE-HF results

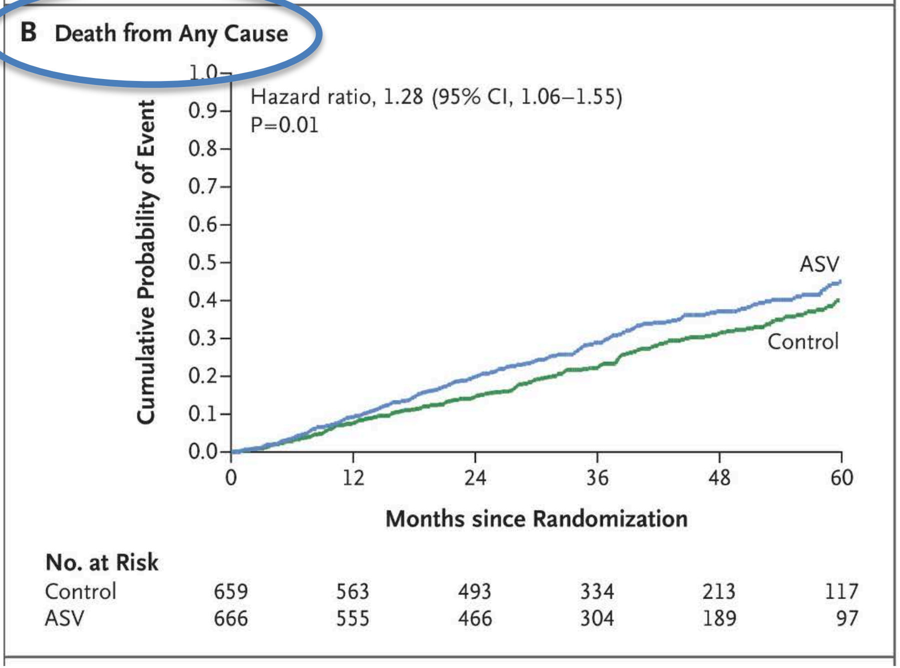


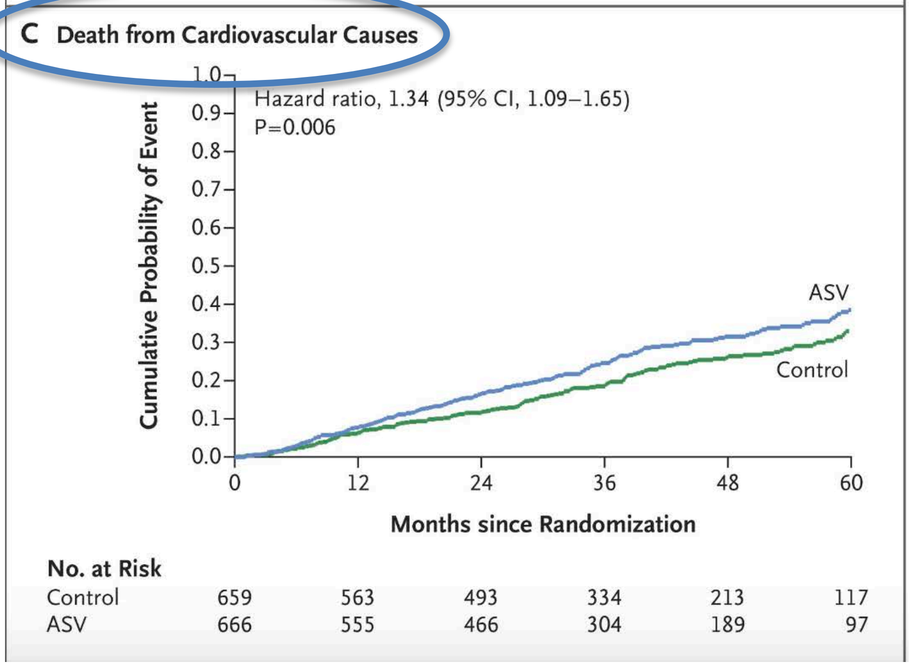
No. at Risk

	0	12	24	36	48	60
Control	659	463	365	222	136	77
ASV	666	435	341	197	122	52

N Engl J Med 2015; 373:1095-1105

SERVE-HF results



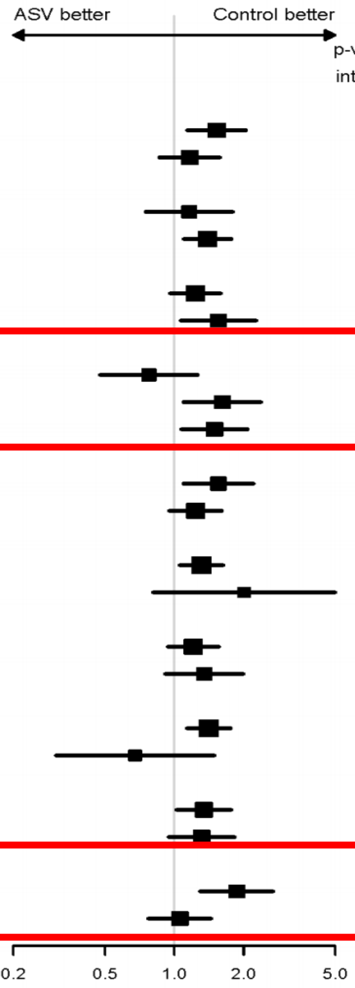


N Engl J Med 2015; 373:1095-1105

Table S3. Average adaptive servo-ventilation device usage over time

	Proportion of patients with average nightly usage – %						Average usage (h/night)
	<1 h	1–2 h	2–3 h	3–4 h	4–5 h	≥ 5 h	
Follow-up							
2 weeks	16.8	6.8	6.8	10.5	12.4	46.8	4.1
3 months	21.7	6.5	8.0	8.8	11.1	43.9	3.9
12 months	29.4	7.3	7.9	7.7	9.4	38.3	3.4
24 months	31.4	7.2	4.9	5.4	11.4	39.8	3.5
36 months	40.1	6.6	3.9	6.6	6.2	36.6	3.2
48 months	38.6	5.9	5.9	5.9	8.5	35.3	3.2
60 months	33.3	2.8	5.6	6.9	11.1	40.3	3.7
Total	26.7	6.7	6.6	8.0	10.5	41.5	3.7

Subgroup	Patients total n	ASV incidence	Control per p-year	p-value for interaction
SDB (AHI events/hour)				0.20
< 30	697	0.105	0.070	
≥ 30	627	0.097	0.084	
NYHA				0.47
= II	389	0.067	0.058	
≥ III	927	0.118	0.086	
Etiology of HF				0.30
ischemic	756	0.121	0.098	
other	539	0.079	0.052	
CSR				0.04
< 20%	237	0.081	0.103	
20-50%	439	0.097	0.061	
> 50%	490	0.122	0.082	
Age (yr)				0.29
< 70	590	0.083	0.054	
≥ 70	735	0.119	0.097	
Gender				0.35
male	1198	0.106	0.081	
female	127	0.067	0.033	
estimated GFR (ml/min/1.73 m2)				0.68
< 60	686	0.139	0.115	
≥ 60	580	0.059	0.045	
Beta blockers				0.08
yes	1223	0.104	0.074	
no	102	0.074	0.110	
BMI (median split)				0.95
< 28	648	0.126	0.095	
≥ 28	660	0.078	0.060	
LVEF (%)				0.01
< 30	326	0.196	0.105	
≥ 30	743	0.069	0.066	



SERVE-HF outstanding questions

- Mechanism for increased mortality
- Device effect or class effect?

Could ASV be offsetting benefits of CSR?

- Increased end expiratory lung volumes → better oxygenation
- Deep breathing increases vagal activity and reduces muscle sympathetic nerve activity
- Hyperventilation prevents respiratory acidosis → beneficial to heart muscle
- Respiratory pump assisting cardiac output
- Deep inspiration may overcome airflow limitations associated with airway edema
- Periodic hypoxia may offset HF associated anemia

Thorax 2012 Apr;67(4):357-60

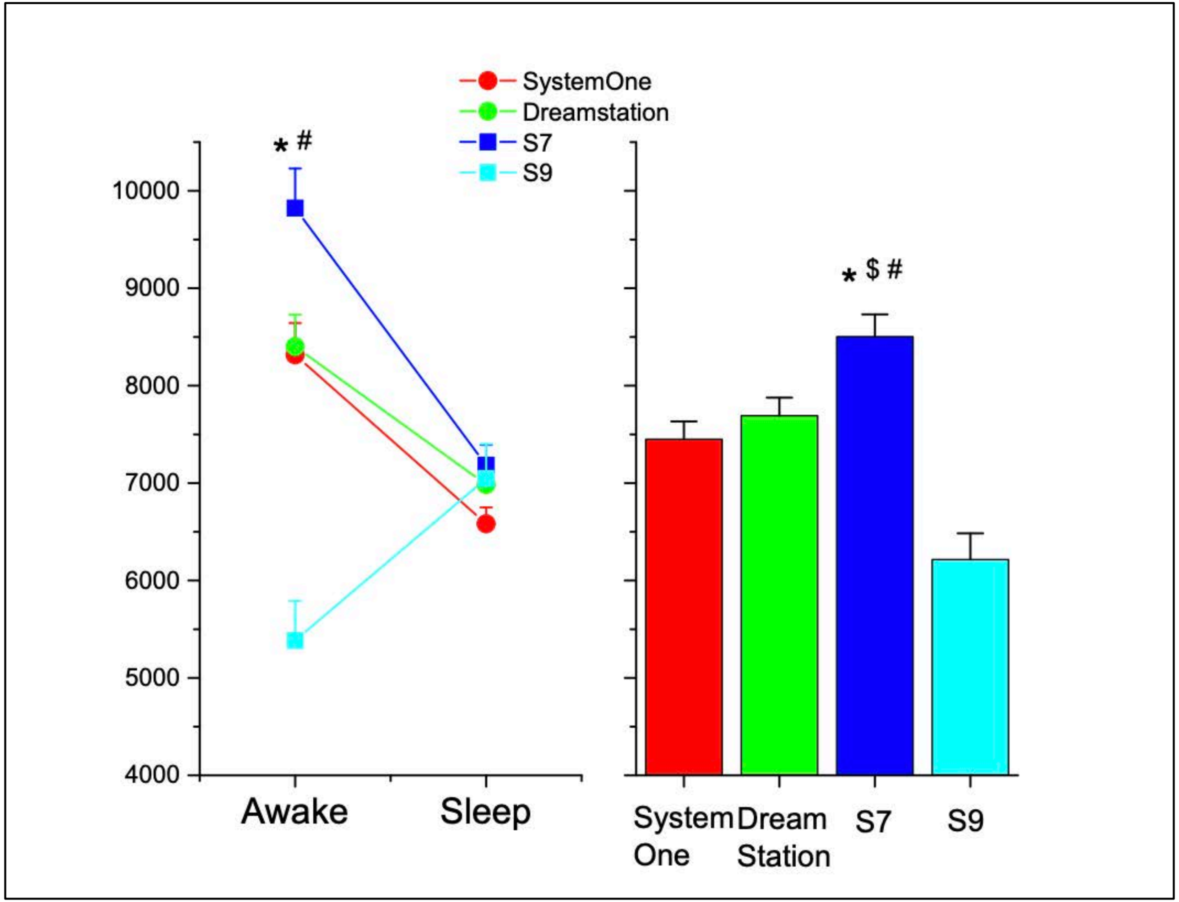
Other potential causes

- ASV led to excess ventilation & respiratory alkalosis→ electrolyte disturbances and arrhythmias
- Device effect or class effect?
  - SERVE HF: used older generation device, fixed EPAP, min PS=3

Device effect or class effect?

- Randomized controlled cross-over physiological experiment
- 14 patients with complex sleep apnea, preserved EF, on ASV
- PSG on 4 nights
- Devices: Resmed S7, Resmed S9, Respironics System one, Respironics Dreamstation

AJRCCM 2019, 199(7): Letter



S7 was 15-40% higher

Since SERVE-HF

- Bad Oeynhausen prospective ASV registry:
- 2004-2013, HFrEF, NYHA ≥ II, EF ≤ 45%, 550 pts, (224 ASV, 326 controls):
  - No effect on survival,
  - Improved HF symptoms,
  - no effect on exercise, LVEF, BNP or ABG's

Clin Res Cardiol 2018;107(8):719-728

Since SERVE-HF

CAT-HF study:

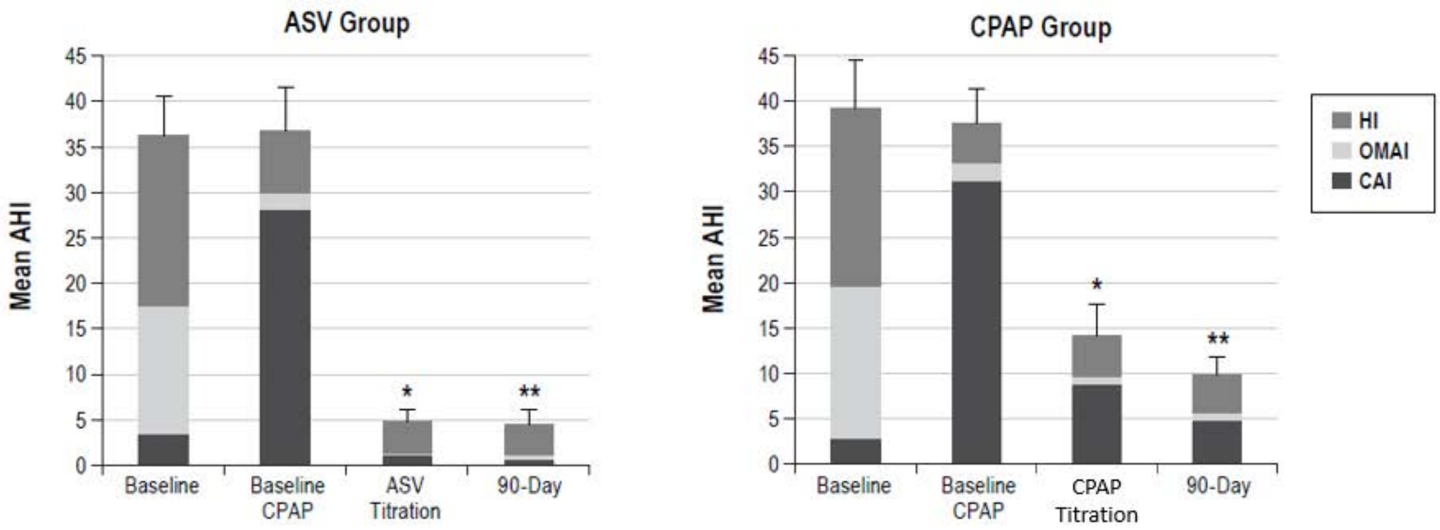
- 126 hospitalized patients with HF and moderate/ severe sleep apnea,
- ASV vs medical therapy alone:
  - no improved CV outcomes at 6 months,
  - subgroup with preserved EF may have benefited (low power)

J AM Coll Cardiol 2017;69(12):1577-1587

ASV for CSA/CSR in CHF SUMMARY

- Currently contraindicated in predominant CSA in CHF with EF $\leq 45\%$ (especially with EF $\leq$ 30%)
- Could be used in CSA/CSR with preserved EF
- SERVE-HF results may be device specific
- Awaiting other studies to determine if class effect (ADVENT-HF)

CPAP vs ASV in TECSA



- ASV achieves AHI < 10 at 90 d; better than CPAP (90% vs 64%)
- Compliance, QoL and ESS similar between CPAP and ASV

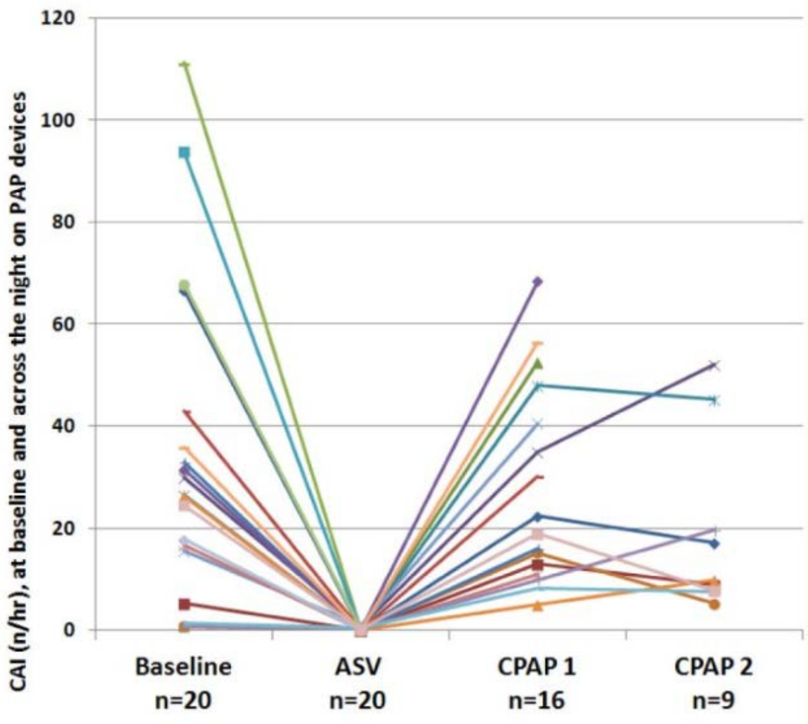
SLEEP 2014;37(5):927-934.

ASV for TECSA SUMMARY

- TECSA is rare and usually transient
- Long term effects unknown but can lead to symptoms
- Optimizing PAP therapy to control TECSA improves sx
- ASV should be attempted in persistent TECSA (TPCSA) despite CPAP

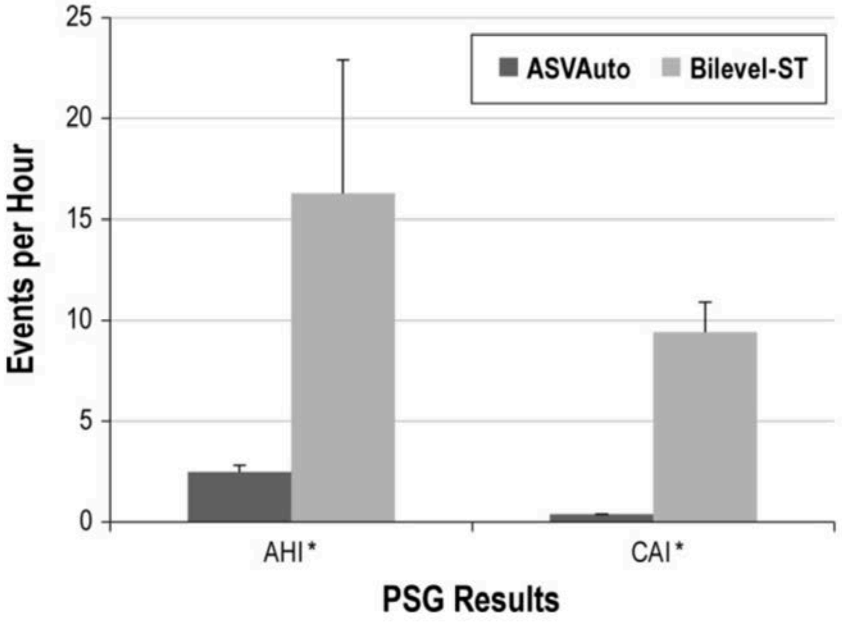
PAP modalities in Opioid related CSA

- CPAP usually ineffective
- ASV more effective at controlling CAI



J Clin Sleep Med 2014;10(6):637-643.

PAP modalities in Opioid related CSA



J Clin Sleep Med 2014;10(8):855-61

Opioid induced CSA summary

- Reducing dose of opioids/weaning off may reverse CSA
- PAP therapies success for Opioid induced CSA:
  - CPAP: 0-54%
  - BPAP ST: 33-66%
  - ASV: 60-100%

Sleep Med Clin 2017;12(4):573-586.

Acetazolamide for CSA

- 2 non-randomized treatment studies reported on the use of acetazolamide for primary CSA
  - 250 mg/day decreased the AHI from 37.2 ± 23.2 to 12.8 ± 10.8 in 14 patients at 1-month follow-up
  - 1000 mg/day - CAI decreased 54 ± 29 to 12 ± 20 in 6 patients after 1 week of therapy
- 1 study in CS/CHF
  - Randomized crossover with reduction in AHI
- Considered a **<u>low evidence level option</u>**
- Side effects: paresthesias, tinnitus, GI symptoms, metabolic acidosis, electrolyte imbalance

Hypnotics for CSA

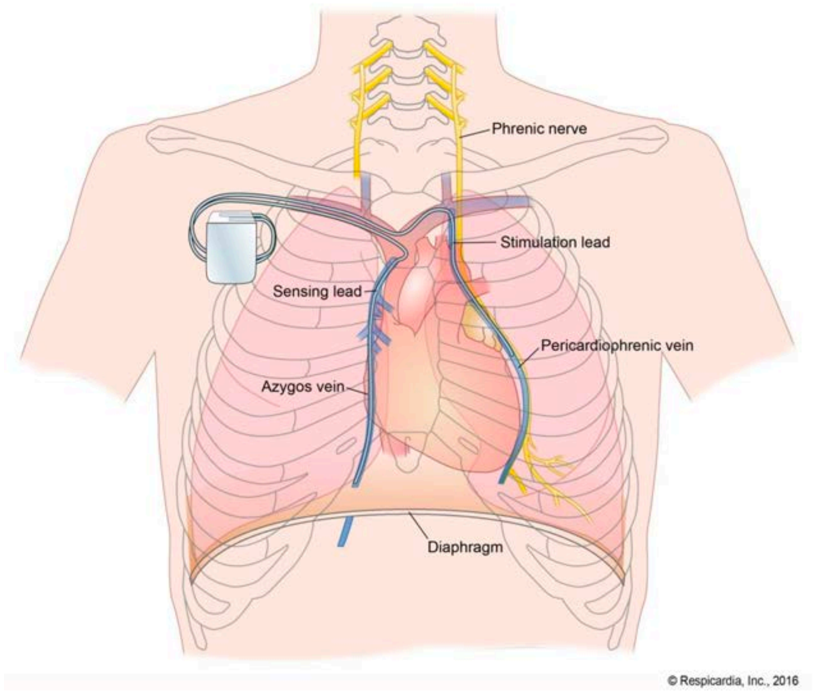
- Zolpidem
  - decreased AHI from 30.0 ± 18.1 to 13.5 ± 13.3 (P = 0.0001) over 9 wks in 20 pts
  - Also has been used in high altitude without much improvement
- Triazolam
  - decreased AHI (P = 0.05), decreased CAI in 5 pts
- **Low evidence level option**

Gases – Oxygen

- Stabilizes respiratory drive
- CPAP + Oxygen reduces SDB
- Oxygen can help CSB
- Problem:
  - Usually cannot justify payment
  - Not as effective as ASV
  - No long term outcome studies

Transvenous Neurostimulation for Central Sleep Apnoea: a Randomised Controlled Trial

Maria Rosa Costanzo, Piotr Ponikowski, Shahrokh Javaheri, Ralph Augostini, Lee Goldberg, Richard Holcomb, Andrew Kao, Rami N Khayat, Olaf Oldenburg, Christoph Stellbrink, William T Abraham



- Randomized 151 pts
  - ITT 68 treatment group, 73 controls
- 50% reduction in AHI
  - Treatment (58) = 51%
  - Control (73) = 11%
- 91% had no serious AE; 37% reported a nonserious AE which resolved in 36% after reprogramming

Methods

- Prospective, multicenter, randomized controlled trial at 31 hospital-based center (university and non- university hospitals)
- 6 in Germany
- 1 in Poland
- 24 in the USA
- Designed by members of the steering committee and the funder in consultation with the US Food and Drug Administration

Eligibility

- 18 years of age
- Before the baseline assessments, patients had to have been medically stable for at least 30 days
- Have to had guideline recommended therapy appropriate for their clinical condition
- Judged by the investigator to be expected to tolerate study procedures and be willing and able to comply with all study requirements
- PSG AHI of at least 20/hr with at least 50% of events being central apneas, at least 30 total central events, and OAI 20% or lower (AASM scoring)

Methods

- All patients had a study visit 1 month after implantation
- The system was activated in the treatment group at the 1-month visit, according to a proprietary algorithm that applied a stimulation pattern that enabled full diaphragmatic contraction while the patient continued to sleep. The ranges of pulse stimulation used were 0.1–10.0 mA for 60–300 µs at 10–40 Hz.
- Follow-up visits and assessments done at the 3-month intervals (until trial end) for a physical examination and to check the implanted device.

Study Design

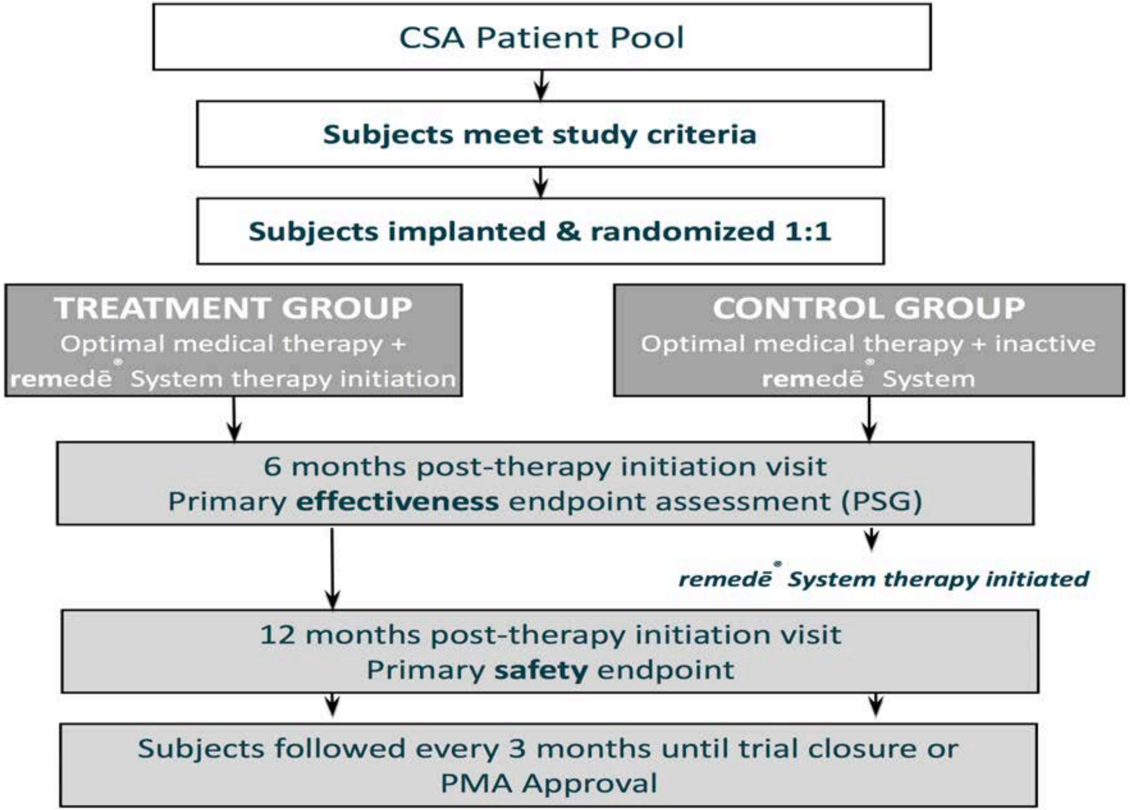
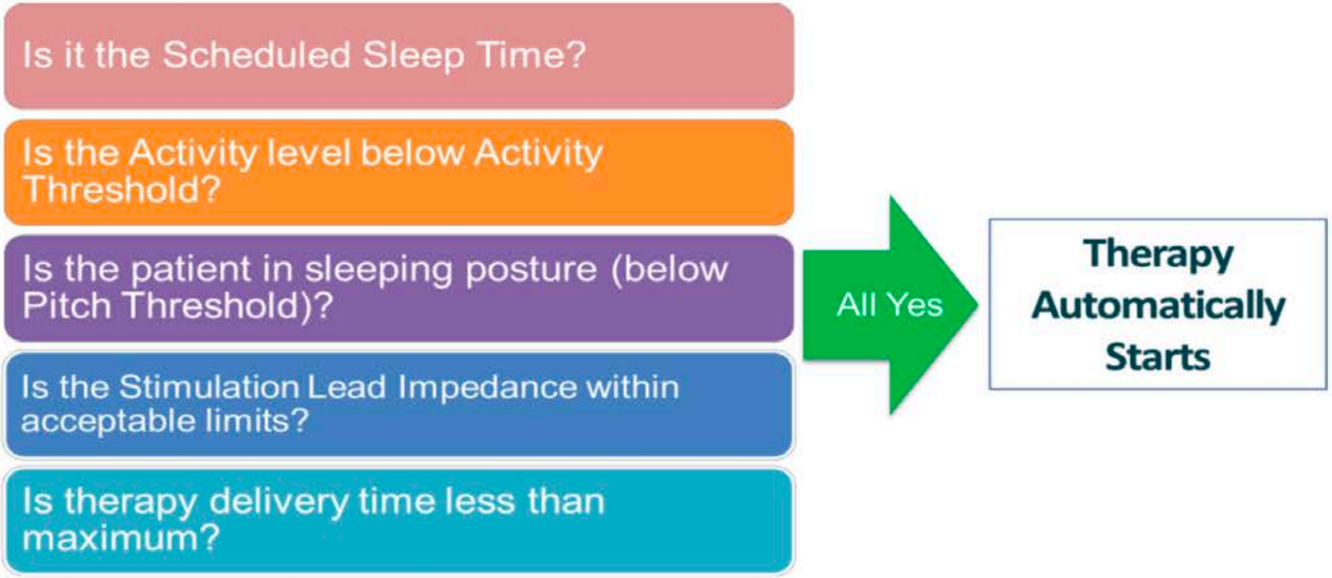


Figure S2. Therapy Algorithm



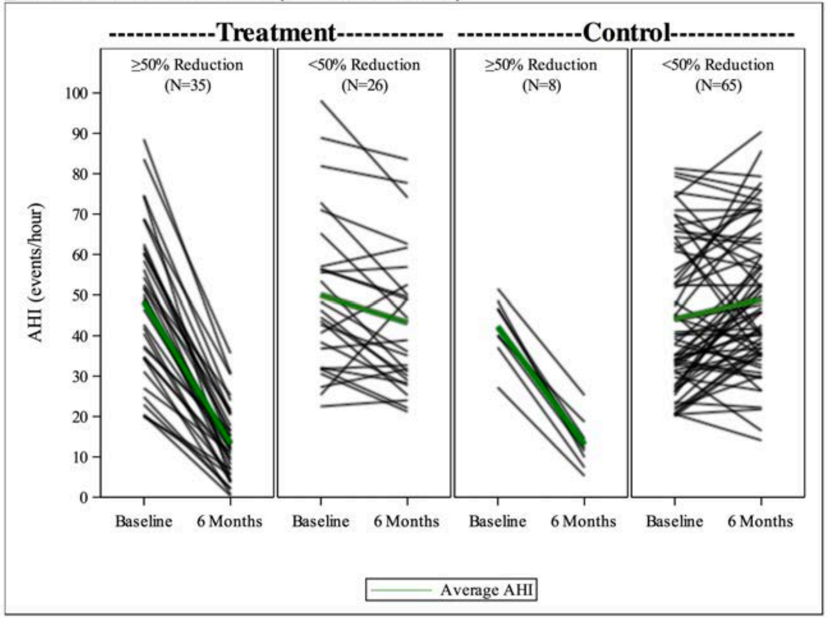
The therapy algorithm used by the **rem**edē® System to provide phrenic nerve stimulation during sleep. The system uses time of day, activity level, and body position (upright or recumbent) to determine a potential sleeping state and, therefore, if stimulation should occur. All these parameters are adjustable and can be tailored to each patient's specific sleeping routine.

	Treatment (n=73)	Control (n=78)	Pooled (n=151)
Age (years)	65 (12)	65 (13)	65 (13)
Male	63 (86%)	72 (92%)	135 (89%)
White	70 (96%)	74 (95%)	144 (95%)
Body-mass index (kg/m²)	30·8 (5·3)	31·3 (6·6)	31·1 (6·0)
Neck width (cm)*	42 (5)	43 (5)	42 (5)
Heart rate (beats per min)	75·4 (12·6)	72·9 (13·8)	74·1 (13·3)
Systolic blood pressure (mm Hg)	125·3 (18·3)	123·7 (17·7)	124·5 (17·9)
Diastolic blood pressure (mm Hg)	74·4 (10·5)	75·3 (11·4)	74·9 (11·0)
Respiration rate (breaths per min)	17·5 (2·9)	17·3 (2·6)	17·4 (2·7)
Apnoea-hypopnoea index (events per h)	48·8 (19·3)	43·7 (16·8)	46·2 (18·2)
Central apnoea index (events per h)	30·0 (18·0)	26·6 (16·1)	28·2 (17·1)
Obstructive apnoea index (events per h)	2·6 (3·2)	2·3 (2·7)	2·4 (3·0)
Mixed apnoea index (events per h)	3·1 (4·1)	2·2 (3·3)	2·6 (3·7)
Hypopnoea index (events per h)	13·1 (11·2)	12·7 (11·6)	12·9 (11·4)
ODI4 (events per h)	43·2 (21·7)	37·5 (17·5)	40·2 (19·8)
Atrial fibrillation	32 (44%)	32 (41%)	64 (42%)
Left ventricular ejection fraction†	39·7 (12·1)	39·4 (12·2)	39·6 (12·1)

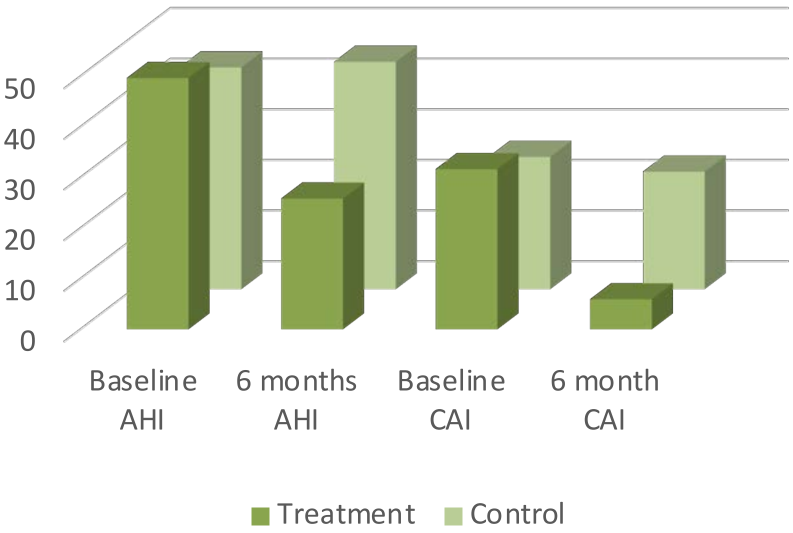
Primary Outcome

	6 months' follow-up		Between-group difference	One-sided p value
	Treatment (N=58)	Control (N=73)		
Primary endpoint				
Patients with ≥50% reduction in apnoea–hypopnoea index from baseline*	35 (51%, 39-64)†	8 (11%, 5-20)	41% (25-54)	<0·0001‡

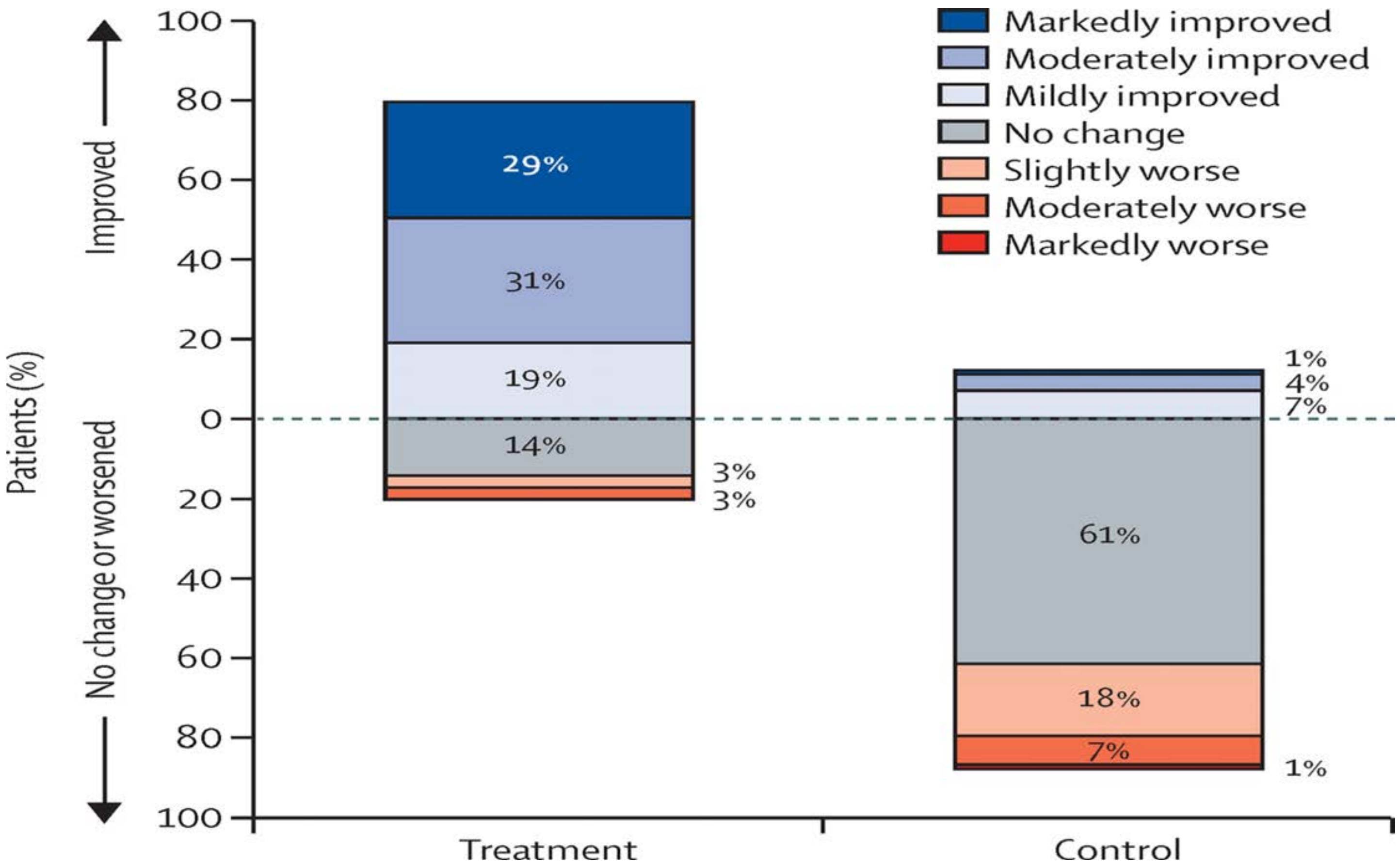
Figure S4. Change in AHI for each Subject by Randomized Group and AHI reduction ≥50% versus <50% reduction (ITT with PSG data)



Treatment SDB Indices



% of pt responses to the pt global assessment



FDA News Release

FDA approves implantable device to treat moderate to severe central sleep apnea

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For Immediate Release October 6, 2017

Release

The U.S. Food and Drug Administration today approved a new treatment option for patients who have been diagnosed with moderate to severe central sleep apnea. The Remedē System is an implantable device that stimulates a nerve located in the chest that is responsible for sending signals to the diaphragm to stimulate breathing.

"This implantable device offers patients another treatment option for central sleep apnea," said Tina Kiang, Ph.D., acting director of the Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices in the FDA's Center for Devices and Radiological Health. "Patients should speak with their health care providers about the benefits and risks of this new treatment compared to other available treatments."

Sleep apnea is a disorder that causes individuals to have one or more pauses in breathing or shallow breaths during sleep. Breathing pauses can last from a few seconds to minutes. Central sleep apnea occurs when the brain fails to send signals to the diaphragm to breathe, causing an individual to stop breathing during sleep for a period of 10 seconds or more before restarting again. According to the National Institute of Health's National Center on Sleep Disorders Research, central sleep apnea can lead to poor sleep quality and may result in serious health issues, including an increased risk for high blood pressure, heart attack, heart failure, stroke, obesity, and diabetes. Common treatment options for moderate to severe sleep apnea include medication, positive airway pressure devices (e.g., continuous positive airway pressure machine), or surgery.

Inquiries

Media

Stephanie Caccomo
301-348-1956

Consumers

888-INFO-FDA

Related Information

- FDA: Recently Approved Devices
- FDA: Premarket Approvals
- FDA: Remede System
- CDC: Sleep disorders

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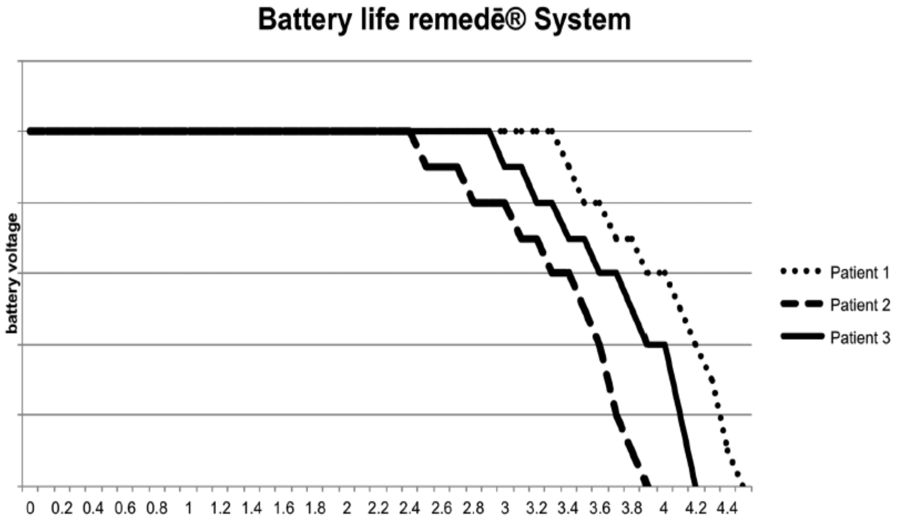
Long-Term Experience with First-Generation Implantable Neurostimulation Device in Central Sleep Apnea Treatment

HENRIK FOX, M.D., THOMAS BITTER, M.D., DIETER HORSTKOTTE, M.D., PH.D., F.E.S.C., F.A.C.C.P., OLAF OLDENBURG, M.D., and KLAUS-JÜRGEN GUTLEBEN, M.D.
From the Clinic for Cardiology, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany

Table I.

Patient Demographics and Clinical at Baseline

	1st Patient	2nd Patient	3rd Patient
Age, years	76	74	77
Gender	Male	Male	Male
BMI, kg/m^2	32.5	29.1	33.2
Heart failure type	HFpEF	HFpEF	HFpEF
NYHA class	2	2	3
Heart rate, beats/min (at rest)	65	55	61
LVEF, %	60	50	60
BNP, pg/mL	163	158	27.5



(PACE 2017; 40:498–503)

Conclusions

- Central sleep apnea most commonly seen in CHF, stroke, treatment emergent PAP therapy and opioid use
- Treatment should be targeted at underlying cause if possible (eg tx of CHF, reduction of opioids)
- TECSA may resolve over time
- ASV most effective in HFpEF, TECSA; less effective in OpCSA; should not be used in HFrEF at this time
- Phrenic nerve pacing may be appropriate for some

Thanks to Shirine Allam and Josh Roland for use of some of their slides