CENTRAL AND COMPLEX SLEEP DISORDER BREATHING

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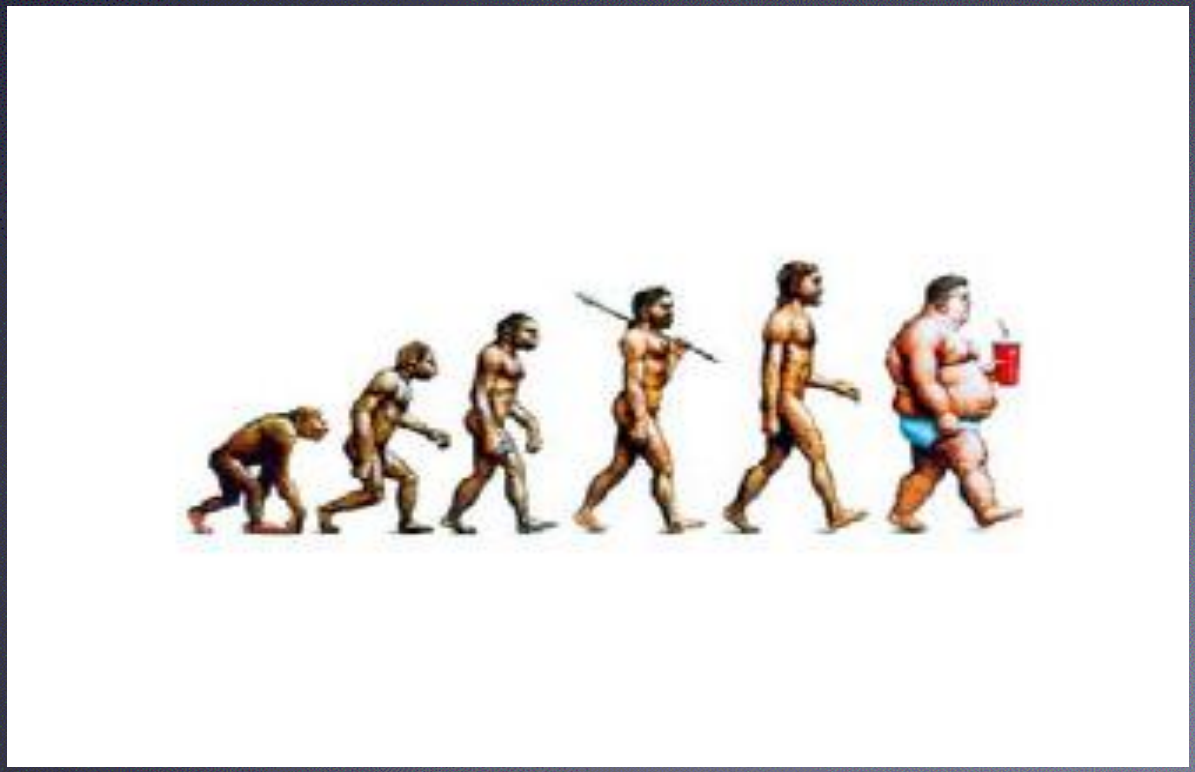
Evolution of Human Race



The Economist, December 2003

Sleep Disorders breathing

- Obstructive Sleep Disorders
- Central Sleep Disorder breathing
- Complex Sleep Disorder Breathing

Control of Breathing at Sleep/Wake

- Transition to Sleep
  - Loss of wakefulness stimulus and behavioral influences
  - Muscle activity and chemoreceptor sensitivity is reduced
- Apnea threshold
- Stable sleep changes – sleep specific CO2 set point
- Transition to Wake - important to restore gas exchange; may cause central apnea:
  - Arousal threshold
  - Ventilatory Response to arousal

Sleep-disordered Breathing:

- New definitions (*AASM 2007*)
  - Cheyne stokes breathing

    3 consecutive cycles of crescendo-decrescendo breathing cycles for at least 10-minutes consecutive or at least at rate of 5 /hour
  - RERA: respiratory-effort related arousal
    - Requires esophageal balloon or Plathesmography
  - Apnea: no airflow for 10 second
  - Hypopnea
    - 30-50% reduction in validated airflow measure
    - Any reduction with 3-4% desats and / or arousal

Central Sleep Apnea

- Lack of drive to breathe during sleep
- Lack of respiratory efforts during cessation of airflow
- Insufficient or absent ventilation leading to compromised gas exchange
- May lead to frequent nighttime awakenings leading to excessive daytime sleepiness and increased risk of adverse CV outcomes

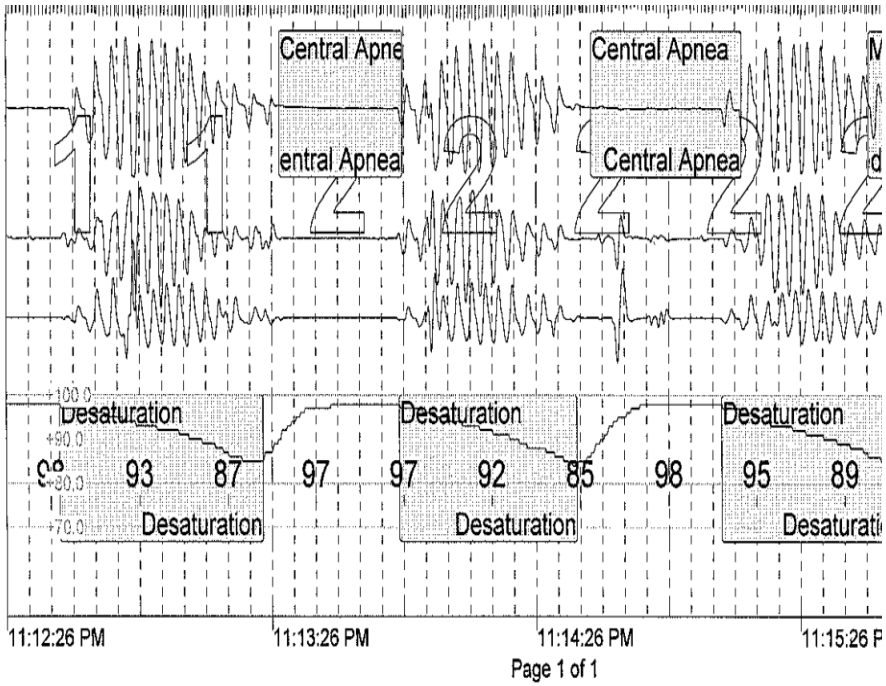
- Most patients have overlap of OSA and CSA
- CSA Syndrome is considered primary diagnosis when $\geq$50% of apneas are scored as central in origin

CSB: Pathogenesis

- Uncertain
- Seen as series of events
  - Patients are hypocapnic to begin with, so to correct hypocapnia, respiratory center initiates an apnea; pCO2 begins to rise.
  - Duration from beginning of apnea until respiratory center detects increasing PaCO2 is prolonged due to increased circulatory time
  - When respiratory center terminates apnea, it is already hypercapnia
  - Hypercapnia causes hyperpnea which causes hypocapnia
- NET EFFECT – oscillation of ventilation between apnea and hyperpnea
- Elimination of hypocapnia with inhaled CO2, CPAP or O2 can attenuate CSB

Cheyne-Stokes Breathing (CSB)

- Cyclic crescendo-decrescendo respiratory effort and airflow during wakefulness and sleep, without upper airway obstruction
- decrescendo effort is accompanied by apnea during sleep, it is a type of central sleep apnea syndrome
- Mainly seen is stage N1 and N2 sleep
- Cycle time – 60-90 seconds (longer than other forms of CSA); correlation with severity of HF
- Arousal typically occurs mid cycle at peak of ventilatory effort
- Most commonly seen in patients with CHF and LV systolic dysfunction



Central SDB- Classification

- Central Sleep Apnea
  - High Altitude Periodic Breathing
  - Idiopathic CSA
  - Narcotic Induced Central Apnea
- Cheyne Stokes Breathing (CSB)
- Obesity Hypoventilation Syndrome (OHS) (Hypercapneic CSA)
- Complex Sleep Apnea

CSA

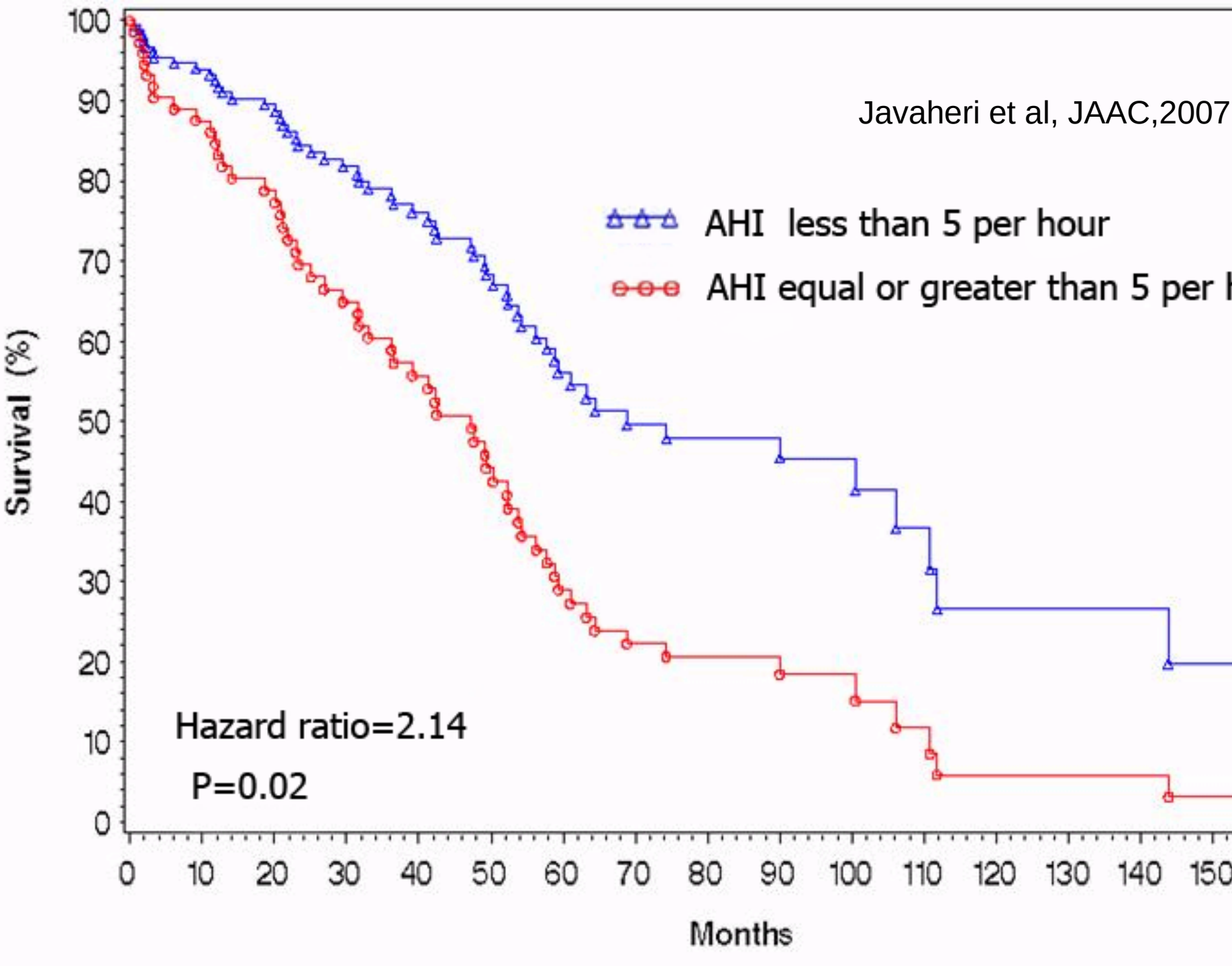
- Hypercapnic – impaired ventilatory output during wakefulness (worsens is sleep as wakefulness stimulus is removed)
  - Impaired Central Drive
  - Impaired Respiratory Motor Control
- Nonhypercapnic
  - Cheyne Stokes Breathing
  - Idiopathic CSA

CSB in Heart Failure-LOOP Gain

- High ventilatory drive (Controller Gain)
- Minimal difference between apnea threshold and sleeping eucapnic PaCO2
- Long circulation time
- Impaired cerebrovascular reactivity to CO2
- Increase pulmonary capillary wedge pressure may stimulate J receptors in lung causing apnea and resultant hyperventilation (Plant Gain)

CSB: Effects

- Intermittent hypoxia – increased sympathetic drive causing arhythmia and worsening of HF
- Arousals – induce adrenergic surges
- Impair systolic and diastolic function
- Extremely negative intrapleural pressure with hyperpnea increase ventricular transmural wall stress and afterload
- CSB in patients with heart failure is associated with higher cardiac mortality
- Clinically
  - Poor sleep quality – sleepiness in daytime
  - Symptoms of worsening heart failure – dyspnea, edema
  - Paroxysmal nocturnal dyspnea (due to hyperpnea)
  - Nocturnal angina, recurrent arrhythmia


Javaheri et al, JAAC,2007
AHI less than 5 per hour
AHI equal or greater than 5 per h
Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Hazard ratio=2.14
P=0.02
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
Months

Hypercapnic CSA

- Lesions of brain stem – tumors, trauma induced lesions
- Congenital Central Hypoventilation Syndrome (Ondine's curse)
- Long term use of Opioids – prolonged periods of hypoventilation with marked hypoxemia and repetitive central apneas; dose dependent effects
- Obesity Hypoventilation Syndrome (OHS)

CSA: Neurologic causes

- Disorders of autonomic system
  - Autonomic dysfunction - Shy Drager Syndrome
  - Familial Dysautonomia
  - Diabetes Mellitus
- Damage to Brain Stem (respiratory centers)
  - Post Polio syndrome
  - Tumor, Infection, Hemorrhage, encephalitis
- Interruption of Neural pathways from medullary respiratory centers to ventilatory muscles
  - Cervical cordotomy

Sleep-Disordered Breathing in Chronic Heart Failure (NYHA II-III)

	Pts (n)	Patients with SDB	Patients with OSA	Patients with CSA
Naughton: Am J Respir Crit Care Med 1995	74	41 (56%)	5 (7%)	36 (49%)
Javaheri: Circ 1998	81	41 (51%)	9 (11%)	32 (40%)
Lanfranchi: Circ 1999	66	46 (69%)	4 (6%)	42 (63%)
Sin: Am J Respir Crit Care 1999	450	316 (70%)	168 (37%)	148 (33%)

Treatment of SDB IN CHF

- Oxygen-40-75%
- CPAP not fully effective
- Non-invasive ventilation (BIPAP-ST)
- Acetazolamide
- Theophyline
- Carbon dioxide
- Lateral sleep position
- Cardiac transplantation
- ASV

CPAP for CS & Heart failure CNPAP trial

- 258 patients
- Mean Age 63+/-10
- Ef 24.5+/- 7.7
- CS AHI 40+/-16
- CPAP 128 Vs 130
- Two year follow up

- NEJM 2005;353:2025-33

- Reduced CSAHI

(-21+/-16 Vs-2+/-18) P<.001

- Reduced nor epinephrine
- EF improved (2.2+/-5.4 Vs0.4+/-5.3)
- Improved 6minute walk distance
- No reduction in mortality,QoL,ANP, hospitalizations

Disordered Breathing Events of 12 HF Patients with Central Sleep Apnea Treated with Acetazolamide

Variable	Baseline	Placebo	ACTZ	*p*
AHI, n/h	55	57	34*†	0.002
CAI, n/h	44	49	23*†	0.004

* $p < 0.05$ versus baseline † = $p < 0.05$ versus placebo

Javaheri, Am J Respir Crit Care Med,2006

Periodic Breathing at Baseline, With Placebo and Theophylline in 15 HF Patients

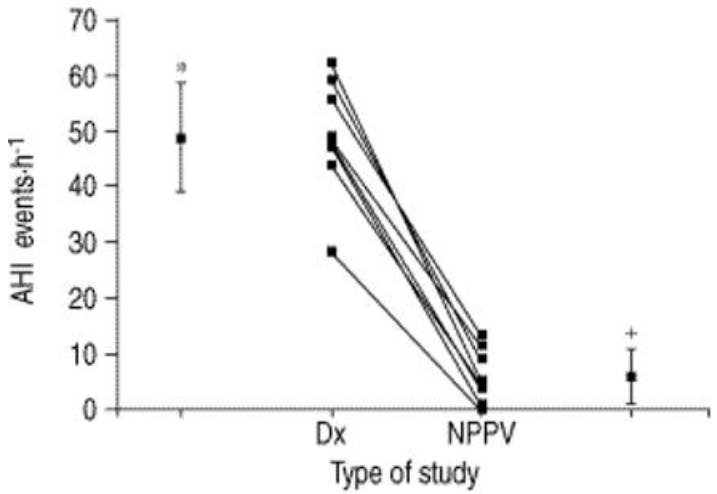
Variable	Baseline	Placebo	Theo
AHI, n/h	47	37	18*
CAI, n/h	26	26	6*
OAI, n/h	2	2	2
MAI, n/h	2	2	1
DBArI, n/h	24	17	8*

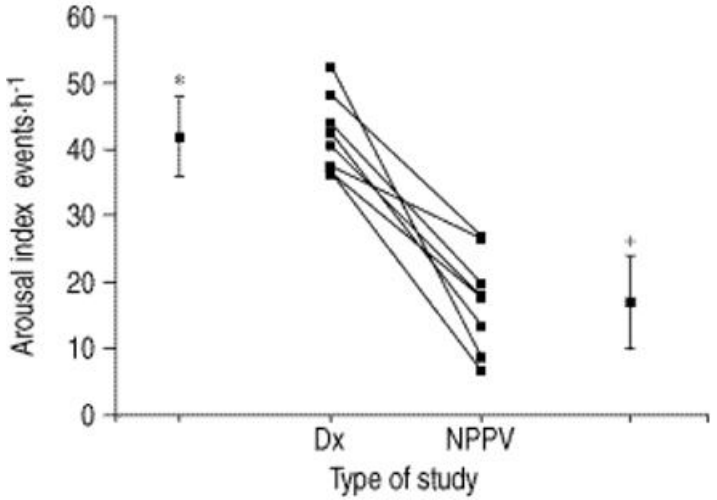
Values are means; * $p < 0.05$

Javaheri et al., NEJM, 1996, 335, 562-7

Noninvasive pressure preset ventilation for the treatment of Cheyne-Stokes respiration during sleep

G.N. Willson[1,3], I. Wilcox[2,3], A.J. Piper[1], W.E. Flynn[1], M. Norman[1,3], R.R. Grunstein[1] and C.E. Sullivan[1,3]



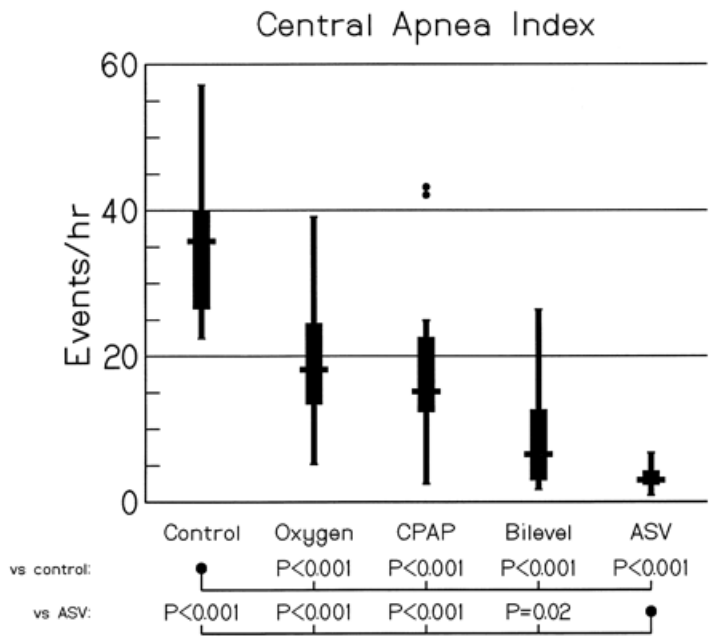


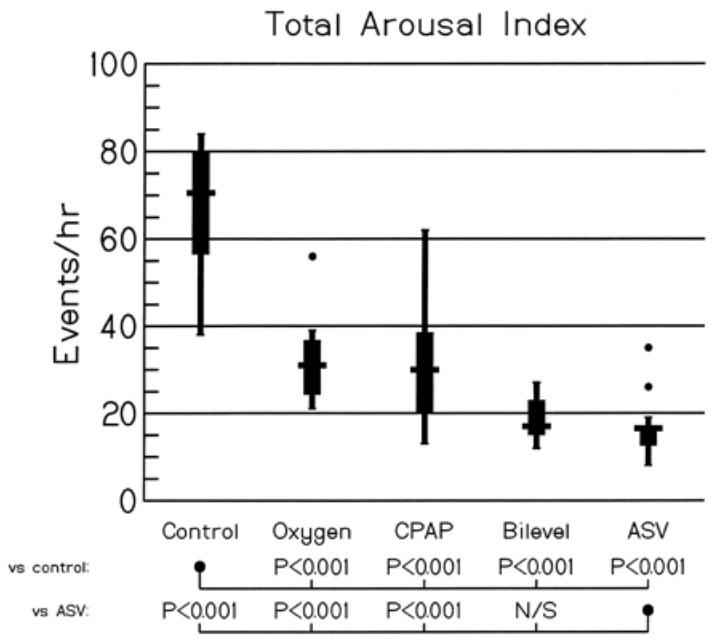
Eur Respir J 2001; 17:1250-1257

Adaptive Pressure Support Servo-Ventilation

A Novel Treatment for Cheyne-Stokes Respiration in Heart Failure

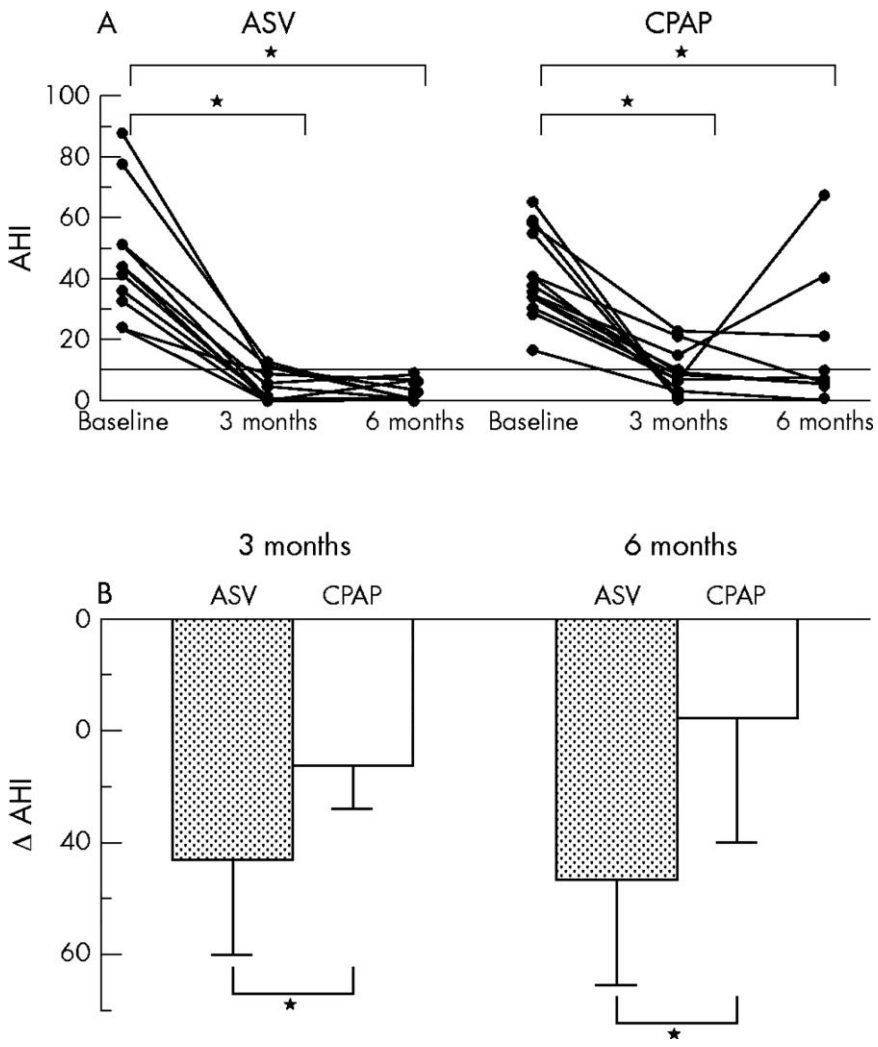
HELMUT TESCHLER, JENS DÖHRING, YOU-MING WANG, and MICHAEL BERTHON-JONES





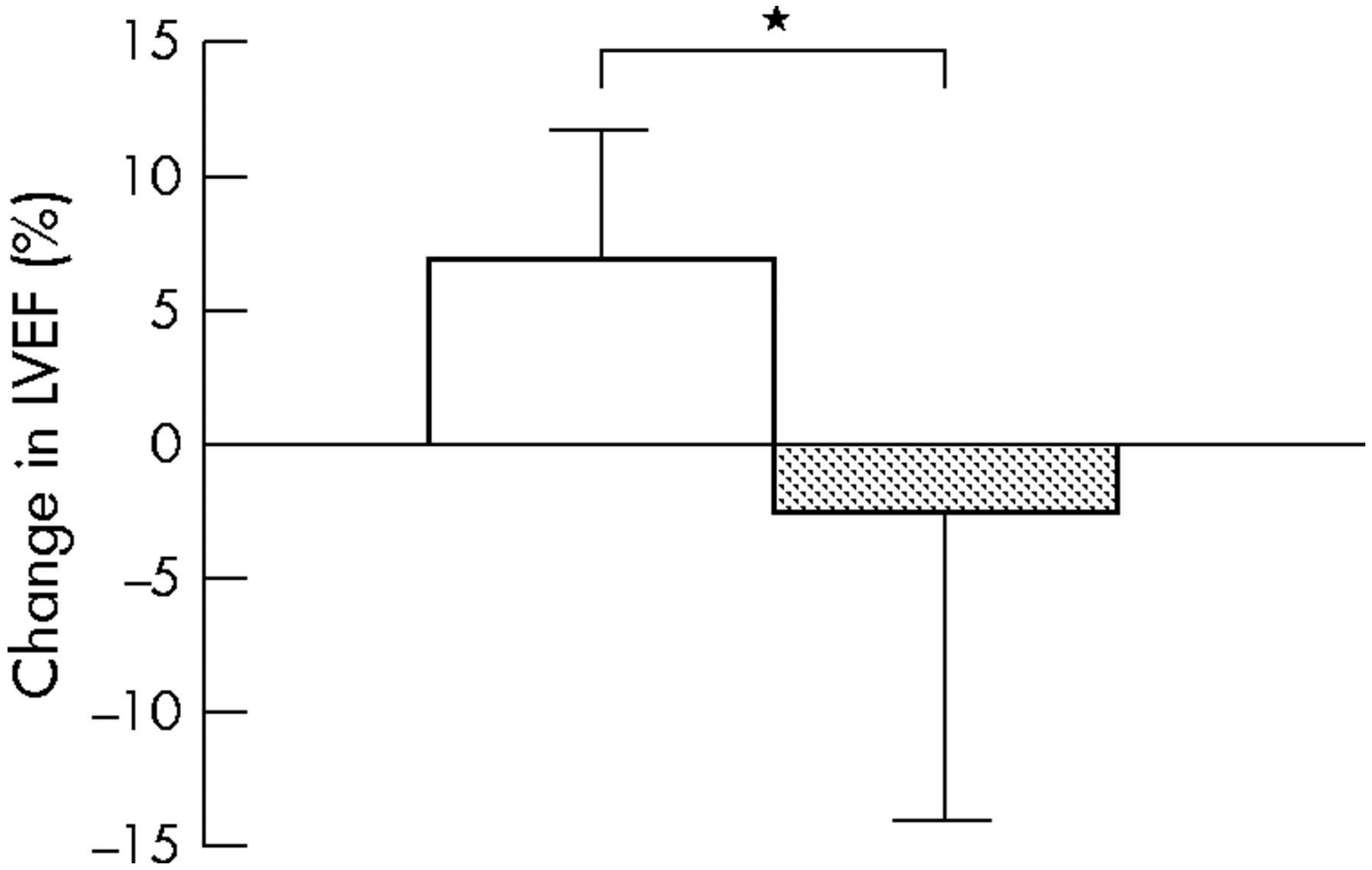
Am. J. Respir. Crit. Care Med., Volume 164, Number 4, August 2001, 614-619

Effect of nocturnal ventilation on apnoea-hypopnoea index (AHI (/h)).



Philippe C et al. Heart 2006;92:337-342

Changes in left ventricular ejection fraction (LVEF) obtained with either ASV or CPAP.



Philippe C et al. Heart 2006;92:337-342

CHF Treatment-Conclusions

- ASV effective in reducing AHI and other parameters
- CPAP partially useful
- Need long term clinical outcome studies- On the way
- Intolerance to devices?

Chronic Opioid use

- Becoming more common for chronic pain (even non malignant disorders)
- Most experts believe – respiratory tolerance develops and respiratory depression is absent or mild
- During wakefulness, chronic respiratory acidosis is absent or mild
- While sleeping, 30-90% patients will have sleep apnea (central or obstructive) – may contribute to mortality

CSA in Chronic Opioid Users

- Develop combination of obstructive and central apnea events (pathogenesis – unknown)
  - Central events mainly in Non REM sleep
  - With PAP therapy, on CPAP obstructive events may be corrected and central events persist
  - When compared to age, gender, and BMI matched controls, higher AHI is due to central events
  - Dose relationship noted with AHI and dose of opioid
- Central Apnea events
  - Periods of apnea and hyperepnea (Biot's respiration)
  - Breaths at end of apnea are abrupt and not gradual
  - Irregular; erratic pattern of respiratory rate and tidal volume

Narcotic Induced CSA: Treatment

- Minimize dose of Narcotics
- PAP therapy
  - CPAP – alone not effective
  - BIPAP S/T
  - Usually require ASV

Complex Sleep Disorder Breathing

Obstructive Sleep-disordered Breathing with a Dominant Cyclic Alternating Pattern—a Recognizable Polysomnographic Variant with Practical Clinical Implications

Robert J. Thomas, MD; Mario G. Terzano, MD; Liborio Parrino, MD; J. Woodrow Weiss, MD

SLEEP 2004;27(2):229-34.

we propose that the CAP-dominant obstructive SDB variant is in part a disorder of respiratory control (perhaps increased loop gain, resulting in a periodic breathing pathophysiology) superimposed on upper-airway obstruction. Treatment of obstruction exposes the respiratory instability and the limitations of PAP in treating this group of patients

Complex Sleep apnea

- Emergent Central sleep Apnea
- CPAP Titration is difficult and Frustrating
- Obstruction still persist with Central events and respiratory instability prominent in NREM Sleep.
- Sleep hypocapnea
- CPAP intolerance and persistent symptoms and elevated AHI.

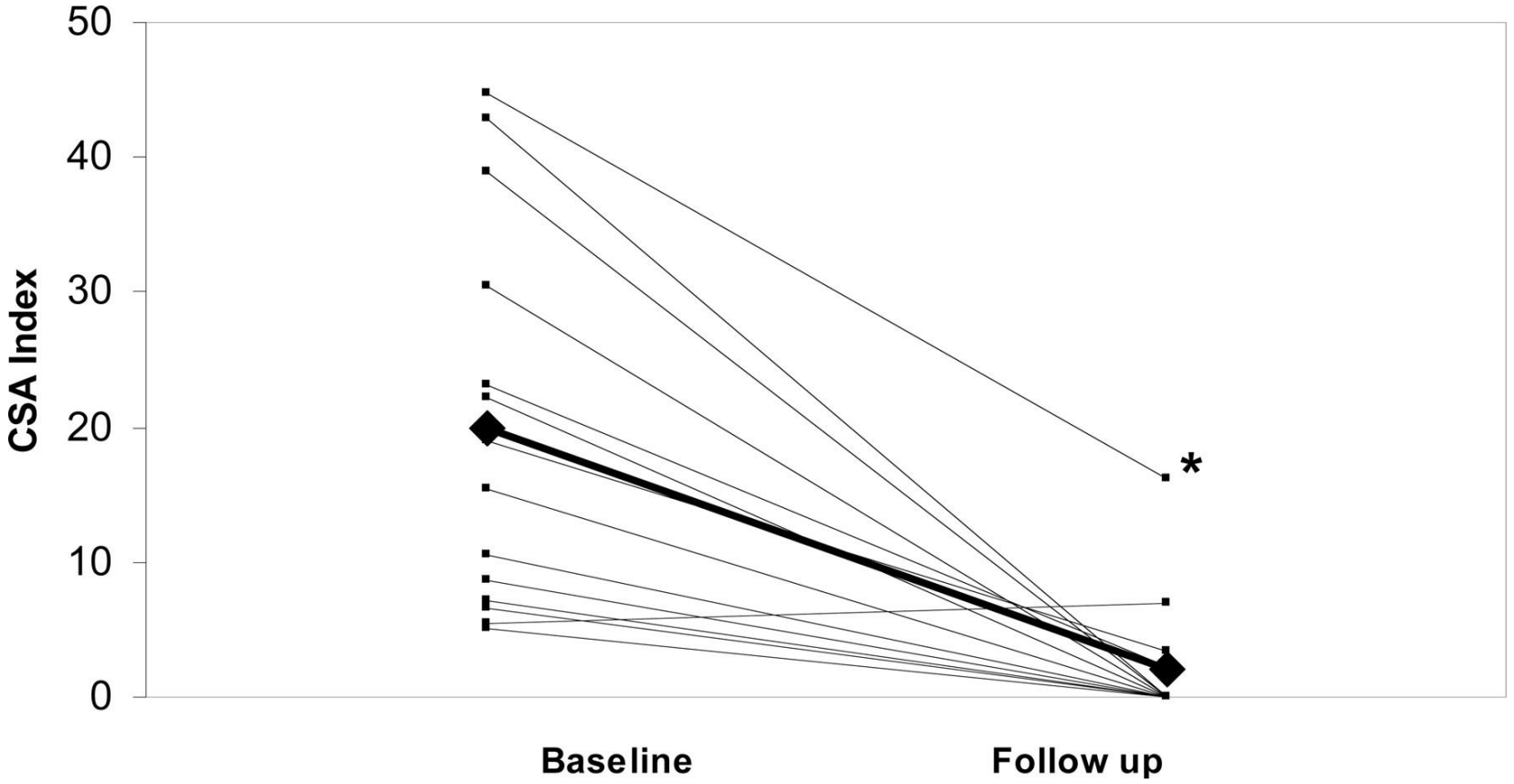
Complex Sleep Apnea Syndrome: Is It a Unique Clinical Syndrome?

Timothy I. Morgenthaler, MD[1,2]; Vadim Kagramanov, MD[3]; Viktor Hanak, MD[2]; Paul A. Decker, MS[4]

- Emergent CSA and CSB with application of CPAP.
- Disruptive sleep and poor CPAP tolerance
- Clinical feature between CSA and OSA, but less insomnia than CSA patients
- Pathophysiology ? Altered chemo reflexes.
- Prevalence of Complex sleep apnea15% in one month study.CSA 0.4% and OSA 84%(n=223)

SLEEP, Vol. 29, No. 9, 2006

Change in CSAI in individual 14 subjects with CPAP-related CSA (diamond sign indicates mean values).



Dernaika T et al. Chest 2007;132:81-87

Complex sleep Apnea is not a Single disease?

Problem	**Solution**
Inadequate titration	retitrate, adjust CPAP level
Overtitration	reduce CPAP level
Substantial mask leak leaving residual events	adjust interface
Treatment-emergent central apnea	wait until it goes away
Residual sleepiness on CPAP	consider modafanil
Change in CPAP requirements due to body weight	lose weight, adjust CPAP level
Sleep transition apneas upon CPAP initiation	observation, consider hypnotic
Narcotic induced central apneas	reduce narcotic dose,
Other causes of sleepiness	increase total sleep time, stimulants

Journal of Clinical Sleep Medicine, Vol. 4, No. 5, 2008

The Prevalence and Natural History of Complex Sleep Apnea

Shahrokh Javaheri, M.D, Jason Smith, R.P.S.G.T, and Eugene Chung, M.D

- Eighty-four of the 1286 patients developed a central apnea index (CAI) of 5 or greater per hour while on CPAP. The incidence of CSA varied from 3% to 10% monthly, with an overall incidence of 6.5%
- 42 of the 84 patients returned for a second CPAP titration. In 33 patients, CSA was eliminated.
- The prevalence of CPAP-persistent CSA was about 1.5%. Severity of OSA, a CAI of 5 or greater per hour, and use of opioids were potential risk factors.

J Clin Sleep Med 2009;5(3):205-211.

Adaptive Servoventilation Versus Noninvasive Positive Pressure Ventilation For Central, Mixed, And Complex Sleep Apnea Syndromes

Timothy I Morgenthaler, MD[1]; Peter C Gay, MD[1]; Nancy Gordon, MS[2]; Lee K Brown, MD[3]

SLEEP 2007;30(4):468-475

Polysomnography Finding	NPPV	ASV	Difference (ASV-NPPV)	P
Respiratory Parameters				
Apnea Hypopnea Index	6.2±7.6	0.8±2.4	-5.4±7.2	0.002
Central Apnea Index	0.6±1	0±0.2	-0.6±1	0.019
Obstructive Apnea Index	0.4±0.9	0±0.2	-0.3±0.7	0.044
Hypopnea Index	5.3±7.3	0.8±2.2	-4.6±7.1	0.008
Respiratory Arousal Index	6.4±8.2	2.4±4.5	-4±6.7	0.012
Mean O_2 Sat	93.9±3.3	94.0±2.4	0.1±1.8	0.842
Oxygen Desaturation Index	4.4±3.9	2.7±4.4	-2.8±6.1	0.053
Sleep Architecture				
Total Sleep Time (min)	344.7±59.2	336.8±43.5	-7.8±53.8	0.513
Sleep Efficiency	79.7±9.2	81±7.6	1.4±9	0.491
Stage 1 (%)	13.2±9.7	13.2±10.1	0.1±6	0.952
Stage 2 (%)	58.7±15.7	60.7±16	2±12.2	0.461
SWS (%)	9.4±9	9.4±9	-1.4±10	0.526
REM (%)	17.4±8.4	16.5±10	-0.8±7.6	0.614
Total Arousal Index	23.9±12.5	24.9±13.2	1±10.2	0.650

± = standard deviation

Complex Sleep Apnea (CompSA)

- Transient and disappear with CPAP therapy in most patients
- Relief of upper airway obstruction may cause change in CO_2 excretion (so $PaCO_2$ falls below apnea threshold)
- Over titration
  - Activation of lung stretch receptors inhibits central respiratory motor input
  - Washout of CO_2 from anatomic dead space
- Increased transitions from sleep to wake as getting used to PAP – CPAP initiation may worsen sleep quality

Questions?

- **what is the mechanism underlying CPAP-induced central apnea?**
- **how/why does the CO2 apnea threshold change over time?**
- **can the upper airway can be stabilized without yielding unstable ventilatory control?**

- How truly refractory cases (central apneas which persist on reassessment) be managed?
- Can the emergence of central apnea (albeit transient) influence long term CPAP adherence by worsening the initial experience with CPAP?
- how/when should the new generation devices which have been developed by industry be used clinically?
- does emergence of central apnea carry any prognostic utility since existing studies are equivocal?2,16

Conclusion-Complex Sleep Apnea

- Carefull titration of CPAP-Accept some OSA events
- Avoid Auto devices
- Clinical Coreation
- ASV ? Coverage ,Resistant patients