# Central sleep apneas: Definition, etiology and evidence based management

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# Overview of the seminar

- Introduction
- Classification of CSA
- Pathophysiology
- **Evidence based management**
- Take home message

# Introduction

- A ***central sleep apnea*** (CSA) results from a transient abolition of central respiratory drive to the respiratory muscles leading to cessation of airflow
- This is most often due to a fall in arterial $PCO_2$ below the threshold required to stimulate breathing
- During a central apnea, there is no respiratory effort and therefore no movement of the chest wall; this is in contrast to obstructive apneas, during which central drive and respiratory efforts continue

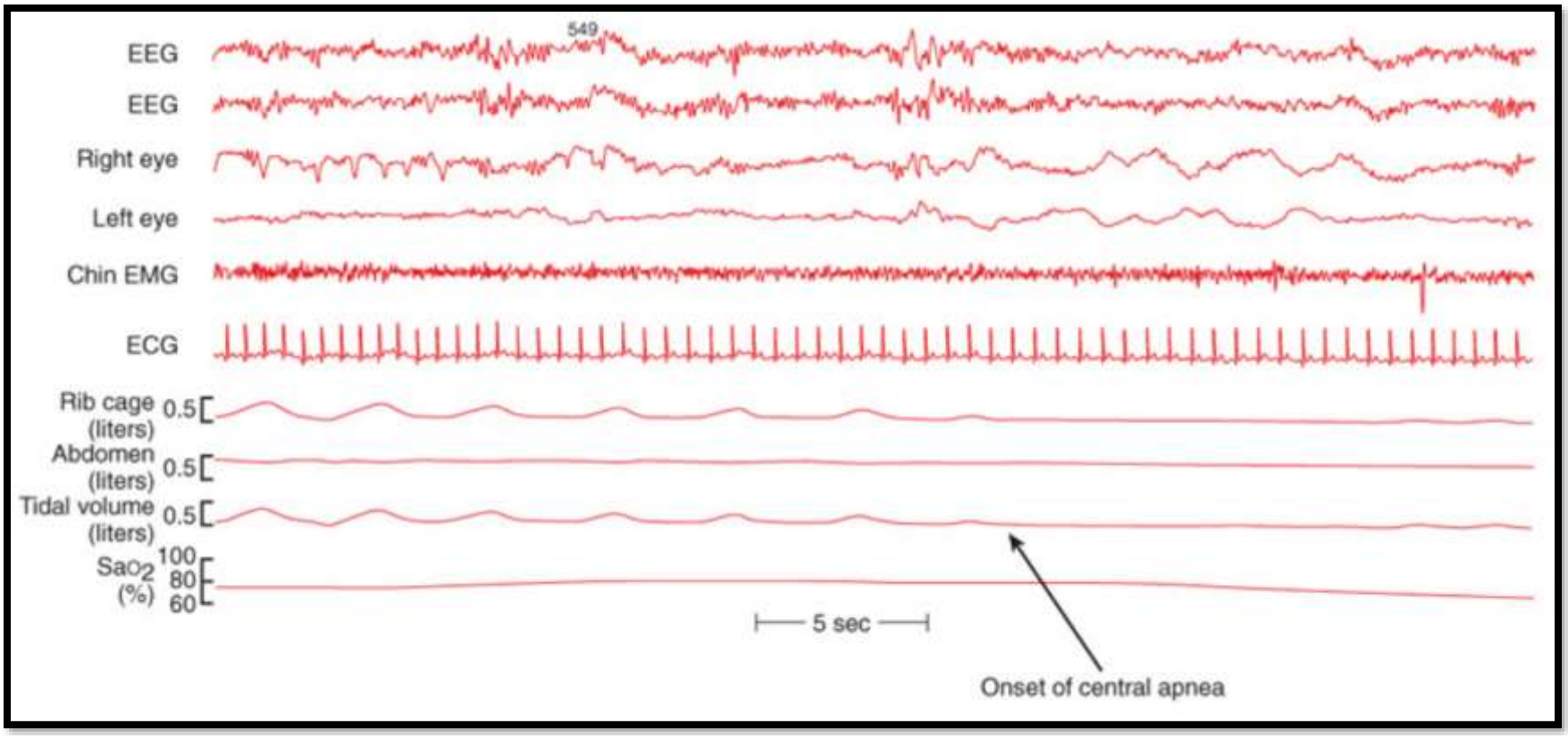
- A **CSA disorder** is defined as recurrent central apneas and hypopneas during sleep
- **CSA syndrome**: CSA disorder accompanied by symptoms, which could include habitual snoring, restless sleep, nocturnal awakenings, morning headaches, insomnia, or excessive daytime sleepiness

# Diagnosis of central sleep apnea

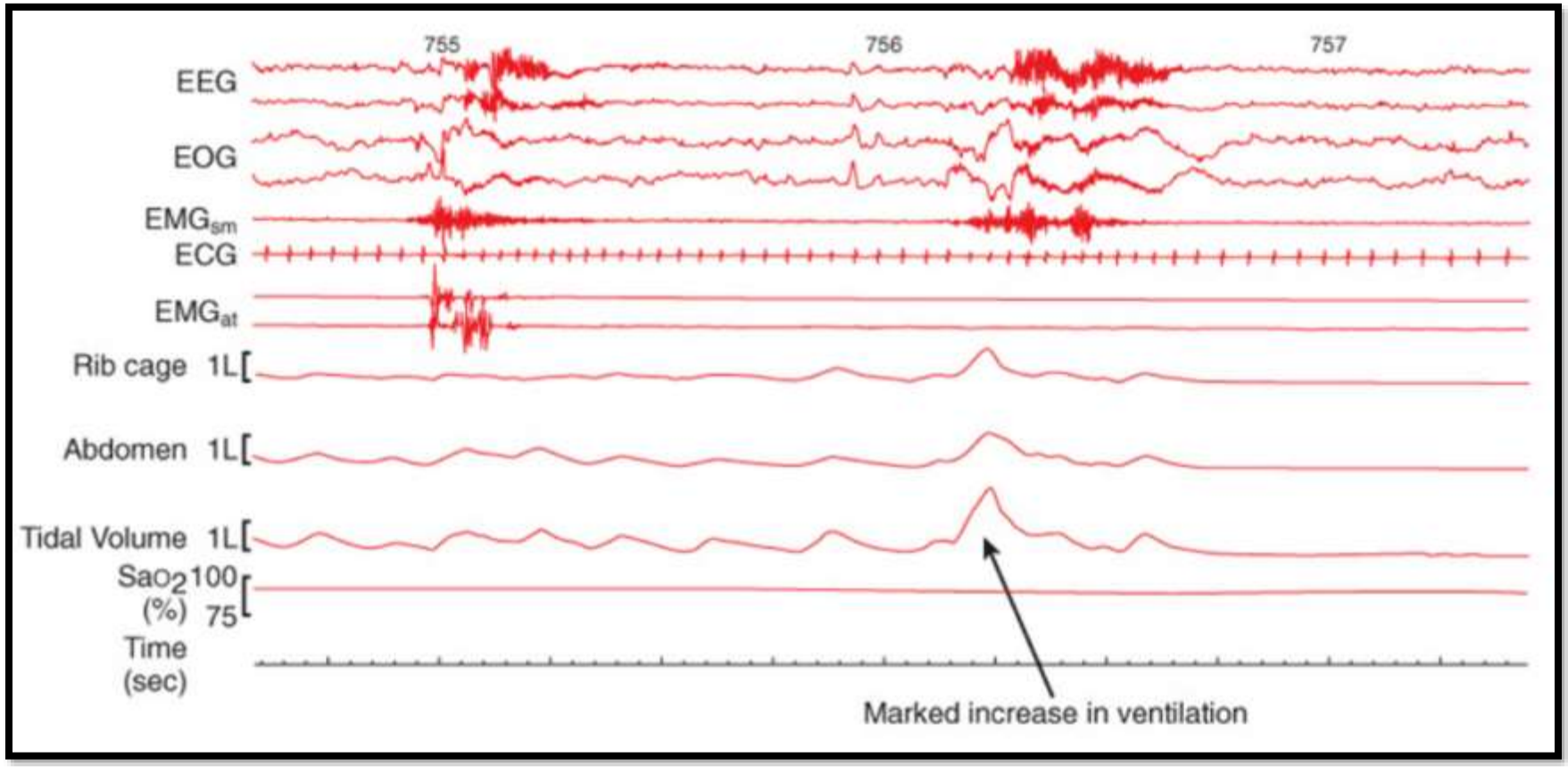
- Full overnight polysomnography with instrumentation capable of detecting respiratory effort and airflow limitation is required to diagnose CSA
- Classification of severity of CSA disorder: an *apnea-hypopnea index* (AHI) of 5 to 15 (mild), 15 to 30 (moderate), or greater than 30 (severe), of which the majority of events are central

- By convention, in adults, apnea is defined as an absence or reduction of airflow to less than 90% of the baseline level for at least 10 seconds
- In case of hypopneas, airflow and tidal volume decrease by 50% to 90% compared with normal breathing for at least 10 seconds usually in association with oxygen desaturation or an arousal from sleep, but without evidence of airflow limitation due to upper airway obstruction

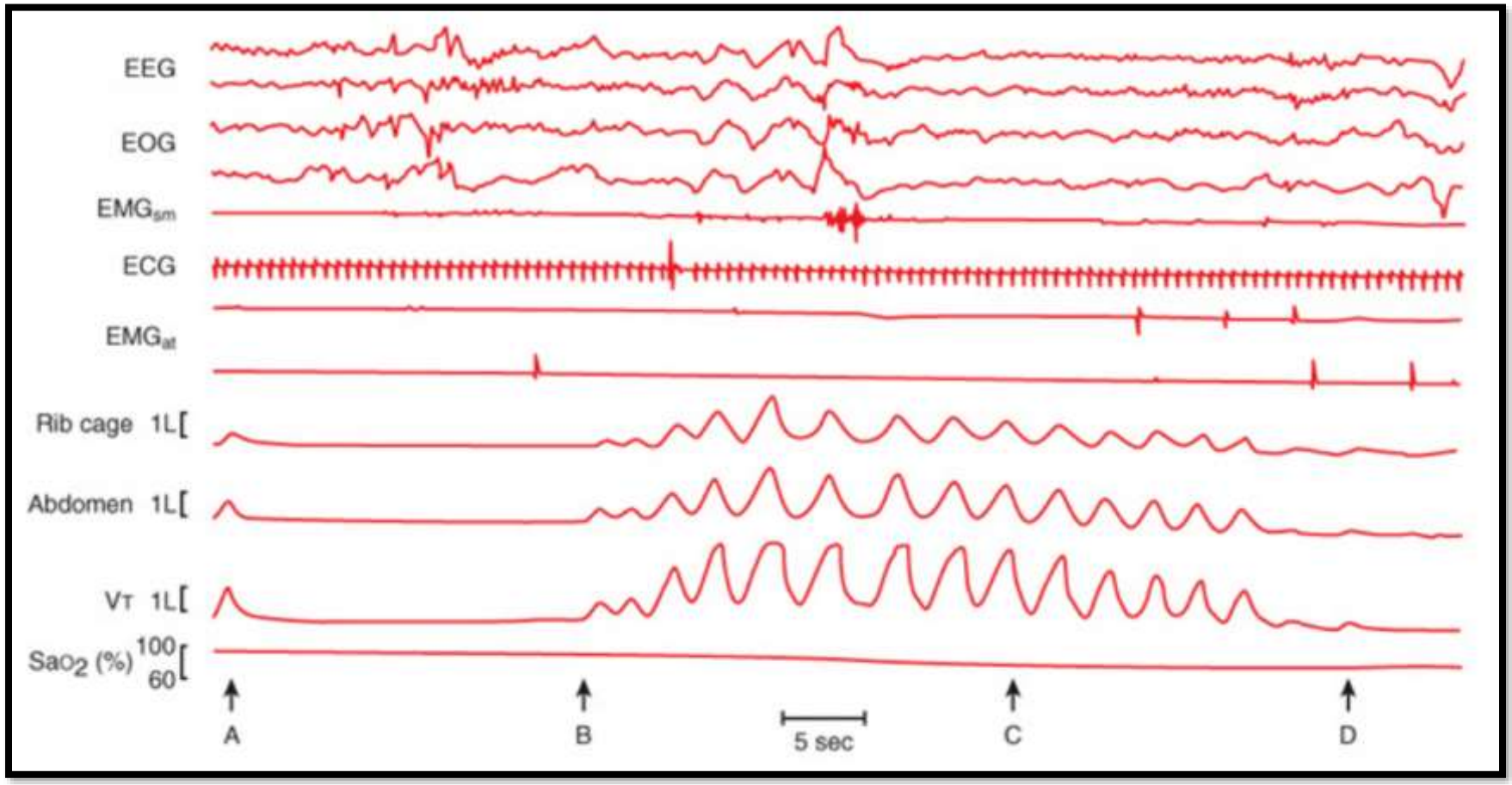
# Hypercapnic central sleep apnea



# Nonhypercapnic central apnea(ICSA)



# Nonhypercapnic central apnea(CSR)



# Classification of Central Sleep Apnea Syndromes(CSAS)

- 6 different forms identified by International Classification of Sleep Disorders (ICSD)
  - (1) Central Sleep Apnea Due to Cheyne Stokes Breathing Pattern
  - (2) Central Sleep Apnea Due to Medical Condition Not Cheyne Stokes
  - (3) Central Sleep Apnea Due to High-Altitude Periodic Breathing
  - (4) Central Sleep Apnea Due to Drug or Substance
  - (5) Primary Central Sleep Apnea
  - (6) Primary Sleep Apnea of Infancy

Westchester, IL: American Academy of Sleep Medicine; 2005

# Classification of central sleep apnea

| | |
|---|---|
| Hypercapnic ($Pco_2 > 45$)<br>(Decreased respiratory drive) | ***Central alveolar hypoventilation***<br>**Secondary**<br>Brain stem tumors, infarcts<br>Bulbar polio<br>Encephalitis<br>**Primary**<br>***Respiratory neuromyopathy***<br>Neuromyopathies<br>Myotonic dystrophy<br>Muscular dystrophy<br>Myasthenia gravis<br>Amyotrophic lateral sclerosis<br>Postpolio syndrome<br>Diaphragm paralysis |
| Nonhypercapnic ($Pco_2 \leq 45$)<br>(Normal or increased respiratory drive) | **Secondary**<br>Congestive heart failure (Cheyne-Stokes respiration)<br>Brain lesions<br>Renal failure<br>Acromegaly<br>Cerebrovascular disease<br>Atrial fibrillation<br>High-altitude periodic breathing<br>Opioid related<br>Complex sleep apnea<br>**Primary**<br>Idiopathic central sleep apnea |

# Pathophysiology

- Underlying pathophysiology: 1) Hyperventilation 2) Hypoventilation
- Post hyperventilation hypocapnia: Underlying pathophysiological mechanism for central apnea associated with CHF, high altitude sickness, and primary CSAS
- These patients chronically hyperventilate in association with hypocapnia during wake and sleep and demonstrate increased chemoresponsiveness and sleep state instability

- Central sleep apnea due to hypoventilation results from the removal of the wakefulness stimulus to breathe in patients with compromised neuromuscular ventilatory control
- Chronic ventilatory failure due to neuromuscular disease or chest wall disease may manifest with central apneas or hypopneas, at sleep onset or during phasic REM sleep
- The ventilatory motor output is markedly reduced and insufficient to preserve alveolar ventilation resulting in hypopneas. Thus, this type of central apnea may not necessarily meet the strict “central apnea” definition

# Central Sleep Apnea Due to Cheyne Stokes Respiration

- Characterized by an absence of air flow and respiratory effort followed by hyperventilation in a crescendo-decrescendo pattern
- CSR most often occurs in patients with congestive heart failure (CHF). The prevalence is estimated to be approximately 30% to 40% in patients with CHF
- This respiratory pattern can also be seen in patients with stroke or renal failure

Bitter T et al, Eur Heart J 2009;11
Javaheri S et al, Circulation 1998;97

- Heart failure patients develop chronic hyperventilation that lowers arterial $PCO_2$ both during wakefulness and sleep and maintains it close to the apnea threshold
- Even small perturbations, such as arousals from sleep that augment ventilation, may be sufficient to drive arterial $PCO_2$below the apnea threshold and trigger central apneas
- Main factor contributing to this instability is increased loop gain so that ventilatory output for a given stimulus is higher than normal

- **CSAS Due to Medical Condition Not Cheyne Stokes**: Can occur in idividuals with Brain lesions, Renal failure, Acromegaly, Cerebrovascular disease, Atrial fibrillation
- **CSAS associated with high altitude** can be seen during the acclimatization period, during or after rapid ascent to high altitudes, typically 4000 meters or greater. Hyperventilation secondary to altitude-associated hypoxia is thought to be the trigger for high-altitude periodic breathing

- **Central Sleep Apnea Due to Drug or Substance** is primarily a disorder related to opioid use
- Patients who are on long-acting opioids for at least 2 months appear to be at increased risk for developing CSAS
- CSAS has been reported to be present in as many as 30% of patients in methadone maintenance therapy

Alattar M et al, Sleep Breath 2009;13
Wang D et al, Chest 2005;128

- Chronic opioid use could cause chronic venous pooling in the capacitance vessels of the splanchnic circulation and legs
- Subsequently, there may be substantial rostral fluid shift on lying down at night that could accumulate in the lungs and stimulate vagal irritant receptors that would provoke hyperventilation and a fall in $PCO_2$ toward the apnea threshold

# Treatment

- *CSAS Due to Congestive Heart Failure (CHF) Including Cheyne Stokes Breathing Pattern (CSBP) and Not Cheyne Stokes Breathing:* Optimizing therapy for heart failure is central to treating CSAS
- CPAP is a therapeutic intervention that is easily available

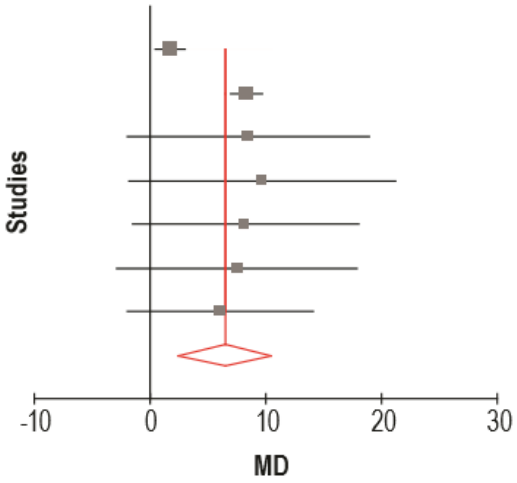
# Effect of CPAP on heart failure

- Application of CPAP in patients of heart failure increases intrathoracic pressure, thereby reducing right and left ventricular volumes(preload),left ventricular transmural pressure(afterload) and work of breathing by unloading the respiratory muscles
- It also augments stroke volume and cardiac output in those with elevated left ventricular filling pressures but has the opposite effect in those with normal or reduced left ventricular filling pressures

Naughton MT, *Am Rev Respir Dis.*145

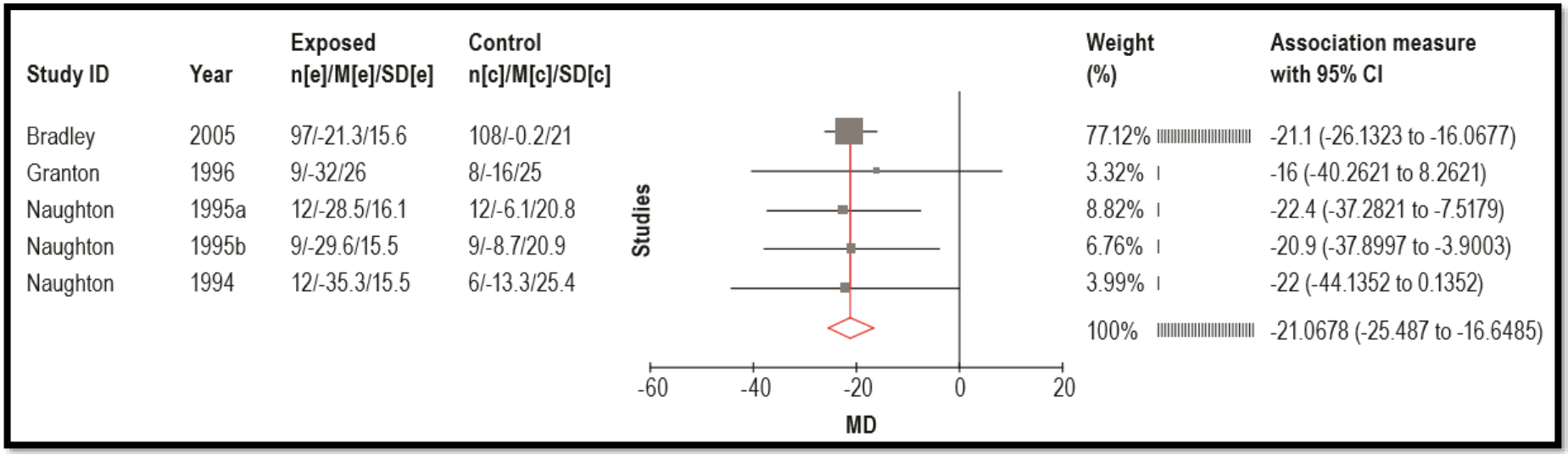
# Meta-analysis of LVEF from controlled CPAP treatment trials

| Study ID | Year | Exposed n[e]/M[e]/SD[e] | Control n[c]/M[c]/SD[c] | Weight (%) | Association measure with 95% CI |
|---|---|---|---|---|---|
| Bradley | 2005 | 128/2.2/5.4 | 130/0.4/5.3 | 24.80% | 1.8 (0.4942 to 3.1058) |
| Sin | 2000 | 14/7.8/2.2 | 15/-0.5/1.5 | 24.73% | 8.3 (6.92 to 9.68) |
| Tkacova | 1997 | 9/8/13.5 | 8/-0.5/8 | 9.51% | 8.5 (-1.9174 to 18.9174) |
| Granton | 1996 | 9/8.6/15.4 | 8/-1.1/7.9 | 8.41% | 9.7 (-1.754 to 21.154) |
| Naughton | 1995a | 12/7.7/15.1 | 12/-0.5/8.4 | 10.28% | 8.2 (-1.5764 to 17.9764) |
| Naughton | 1995b | 9/6.5/12 | 9/-1/10.5 | 9.51% | 7.5 (-2.9174 to 17.9174) |
| Naughton | 1994 | 10/4.6/7.9 | 4/-1.5/6.5 | 12.75% | 6.1 (-1.9343 to 14.1343) |
| | | | | 100% | 6.4577 (2.3979 to 10.5175) |



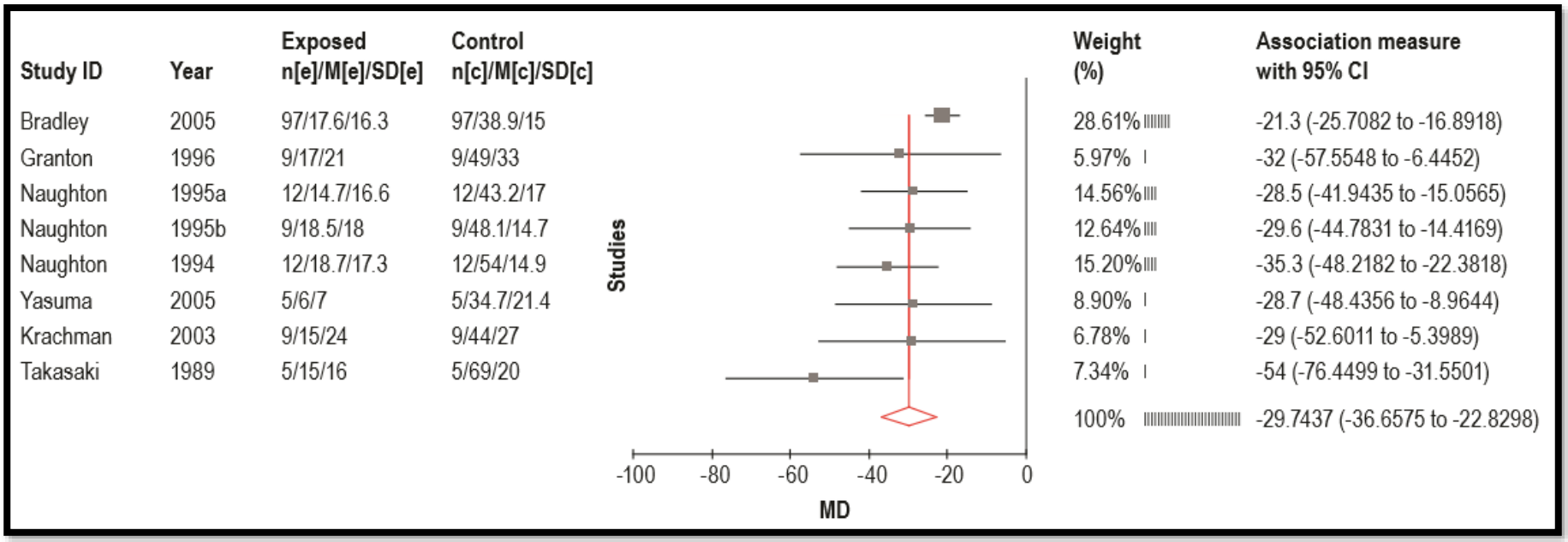

The random-effects meta-analysis showed that CPAP increased LVEF by 6% [95% CI 2.4 to 10.5%] on average when compared with the control group

# Meta-analysis of AHI from controlled CPAP treatment trials




The random effects meta-analysis showed that CPAP decreased AHI by 21/h [95% CI: 17 to 25] over controls

# Meta-analysis of AHI from before-after CPAP treatment trials




CPAP reduced AHI by 30/h [95% CI: 23 to 37] with treatment compared to baseline

# Mechanism of CPAP on reducing AHI

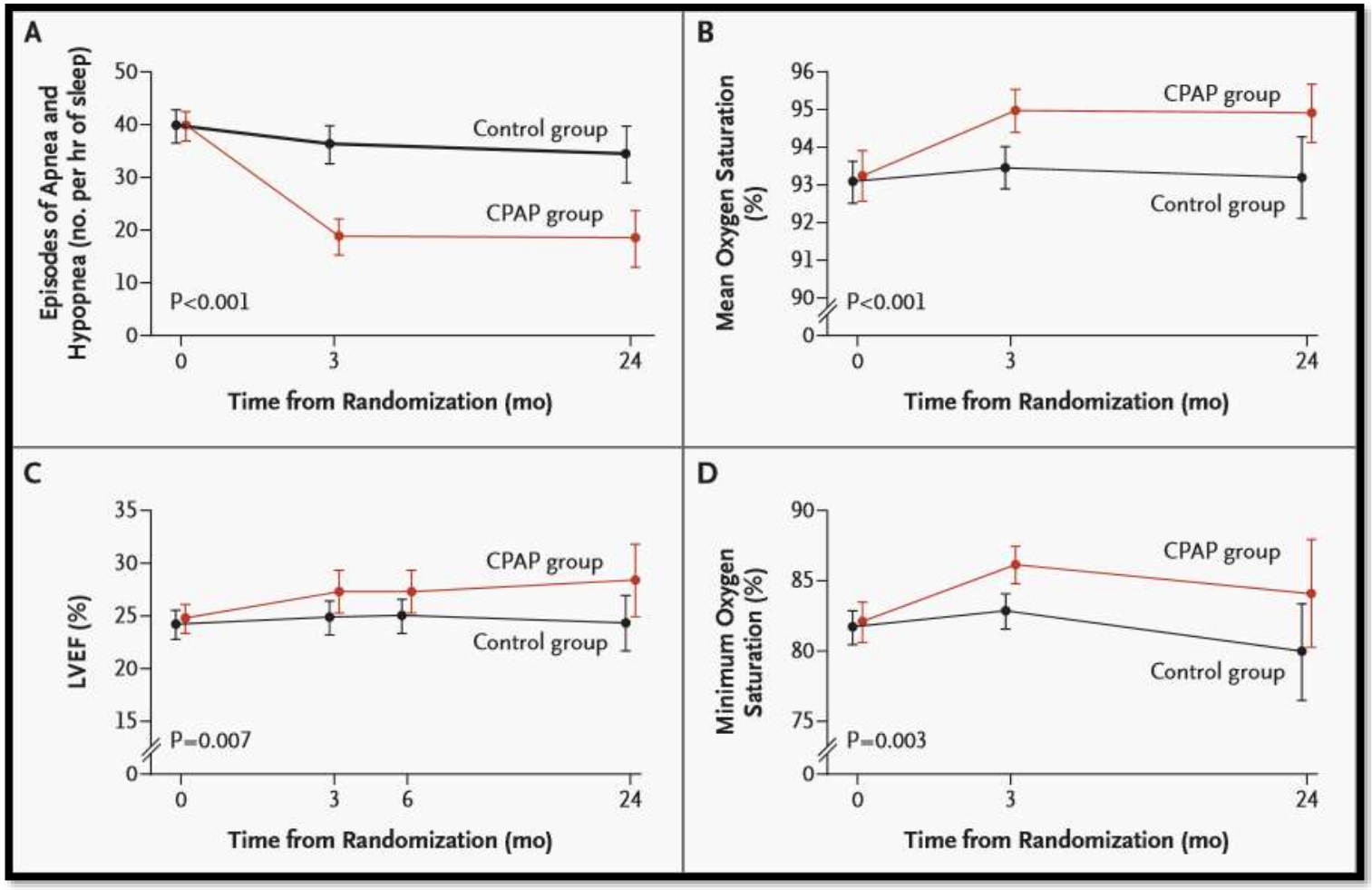
- Raises lung volume, thereby increasing the lung $O_2$ reservoir and thus dampening fluctuations in $PaO_2$
- Reduces lung water and thus pulmonary irritant receptor stimulation

# CANPAP Trial

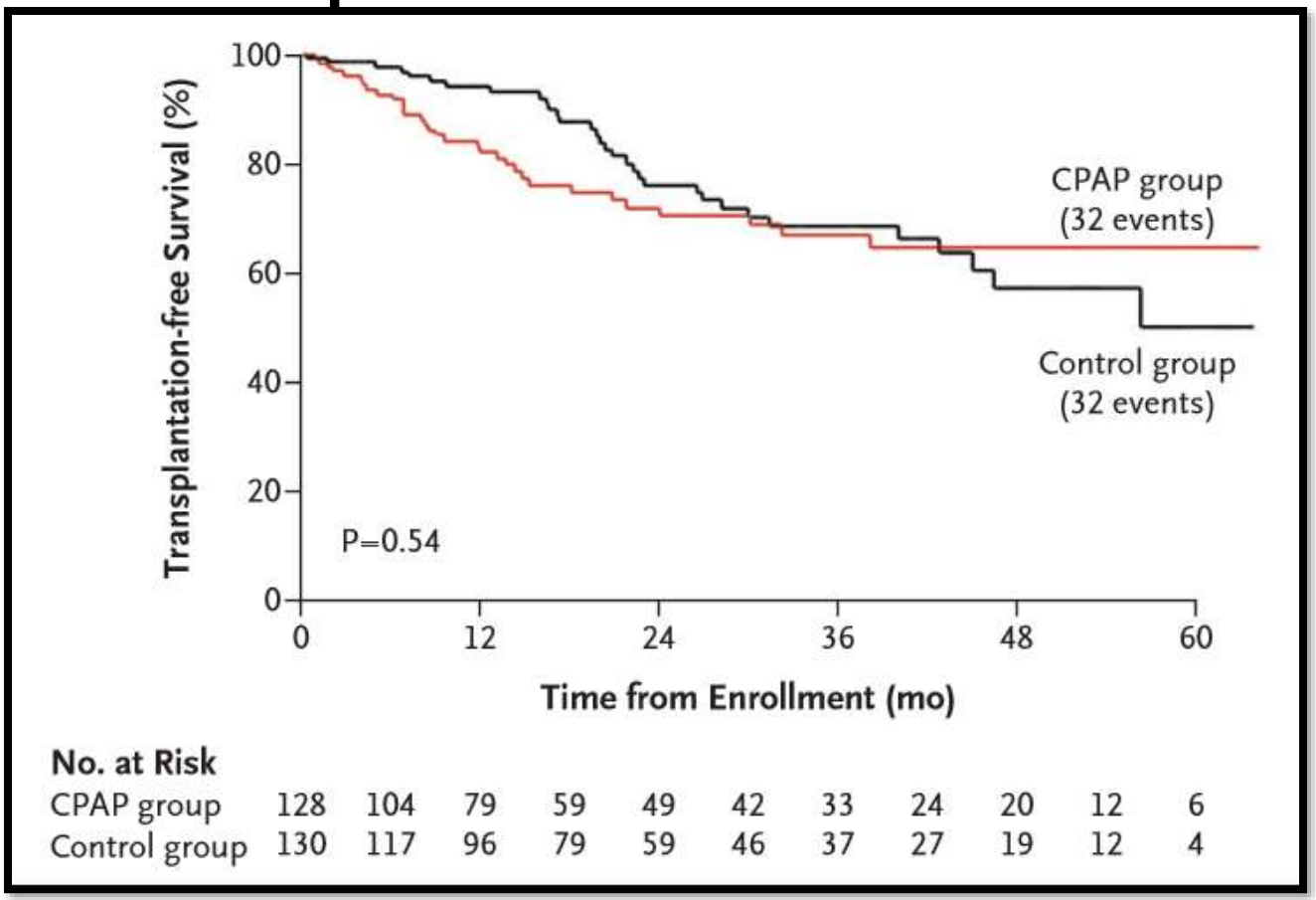
- The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial tested the hypothesis that continuous positive airway pressure (CPAP) would improve the survival rate without heart transplantation of patients who have central sleep apnea and heart failure
- After medical therapy was optimized, 258 patients who had heart failure (mean age [±SD], 63±10 years; ejection fraction, 24.5±7.7 percent) and CSA (AHI= 40±16) were randomly assigned to receive CPAP (128 patients) or no CPAP (130 patients) and were followed for a mean of two years

*Bradley TD et al, N Engl J Med* 2005

# Effect of CPAP on study variables



# Heart transplantation free survival

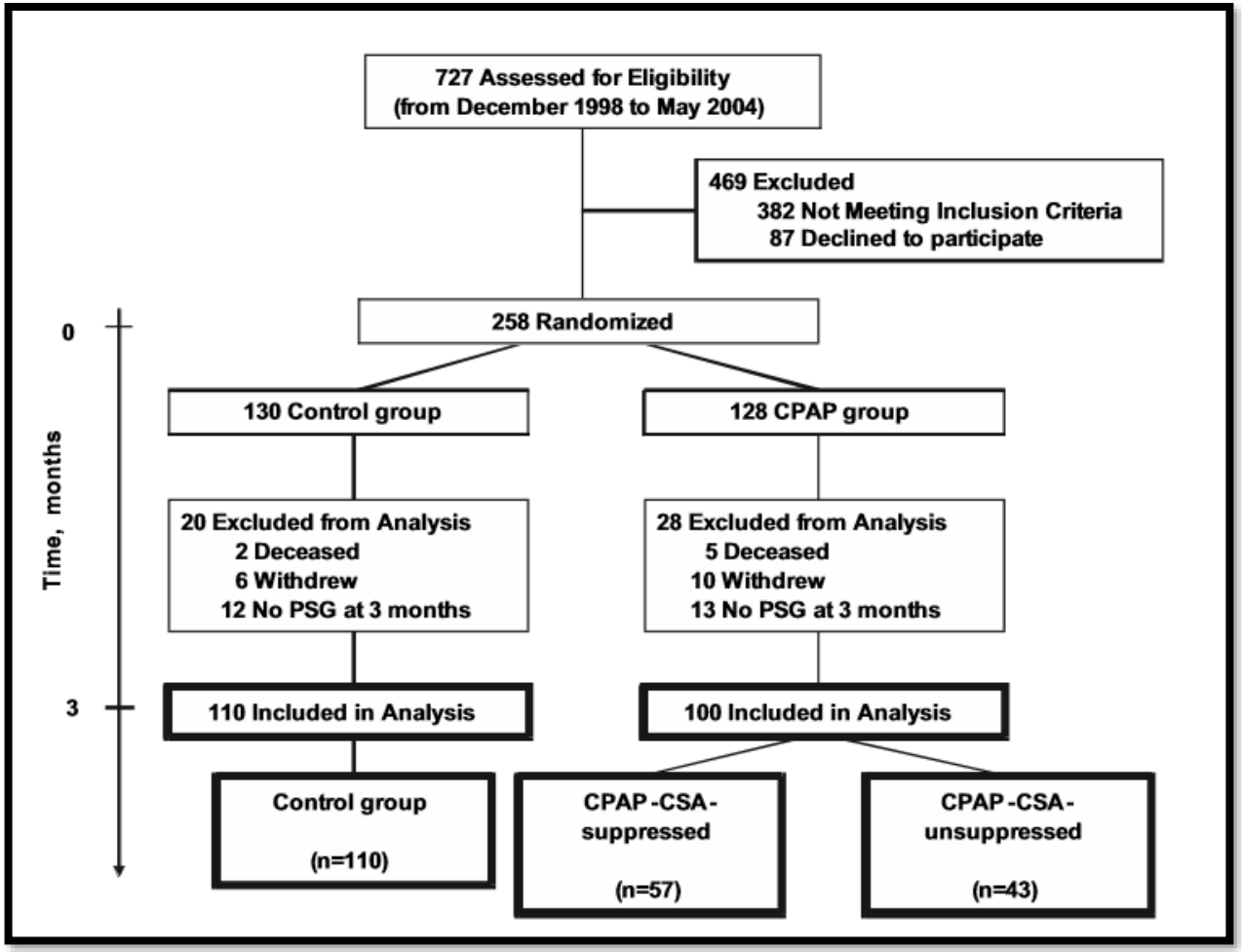


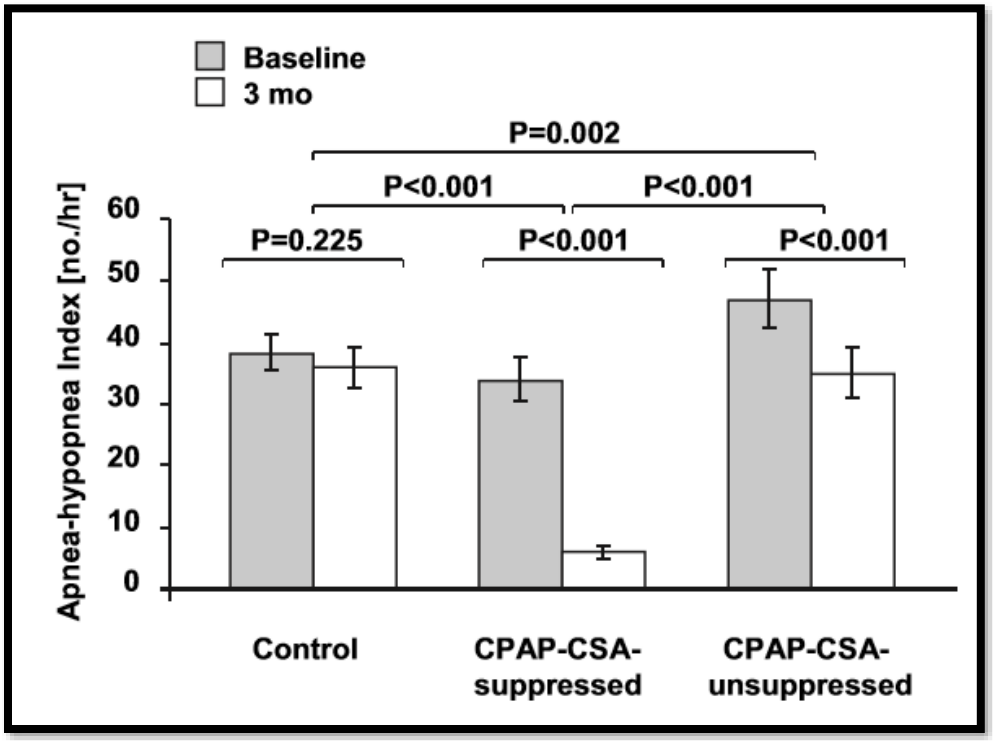

There was no difference in transplantation-free survival rates between the control group and the CPAP group (hazard ratio for transplantation-free survival, 1.16; P=0.54). However, there was an early divergence in the event rates that favored the control group (hazard ratio for transplantation-free survival, 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)

# Outcomes from the trial

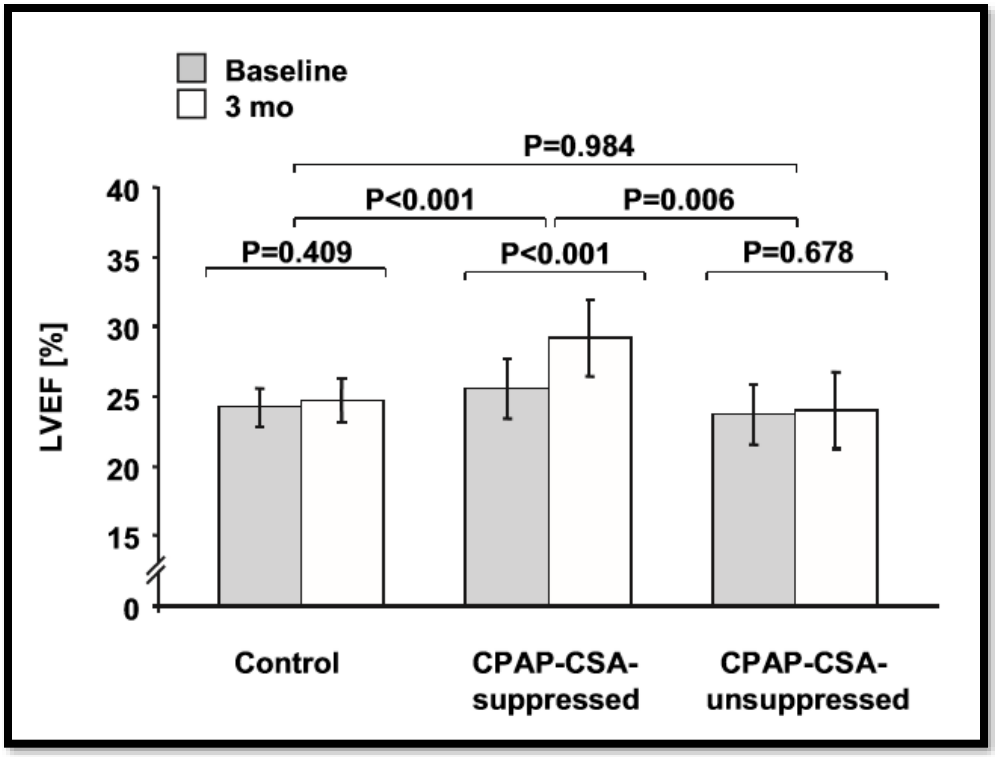
- The trial confirmed the findings of previous small, short-term trials that CPAP attenuates CSA, improves nocturnal oxygenation and LV systolic function, and lowers plasma norepinephrine levels, and it showed that these effects are sustained with long-term therapy
- The trial failed to demonstrate any beneficial influence of CPAP on transplantation-free survival, number of hospitalizations, or quality of life

# Post hoc analysis of CANPAP trial



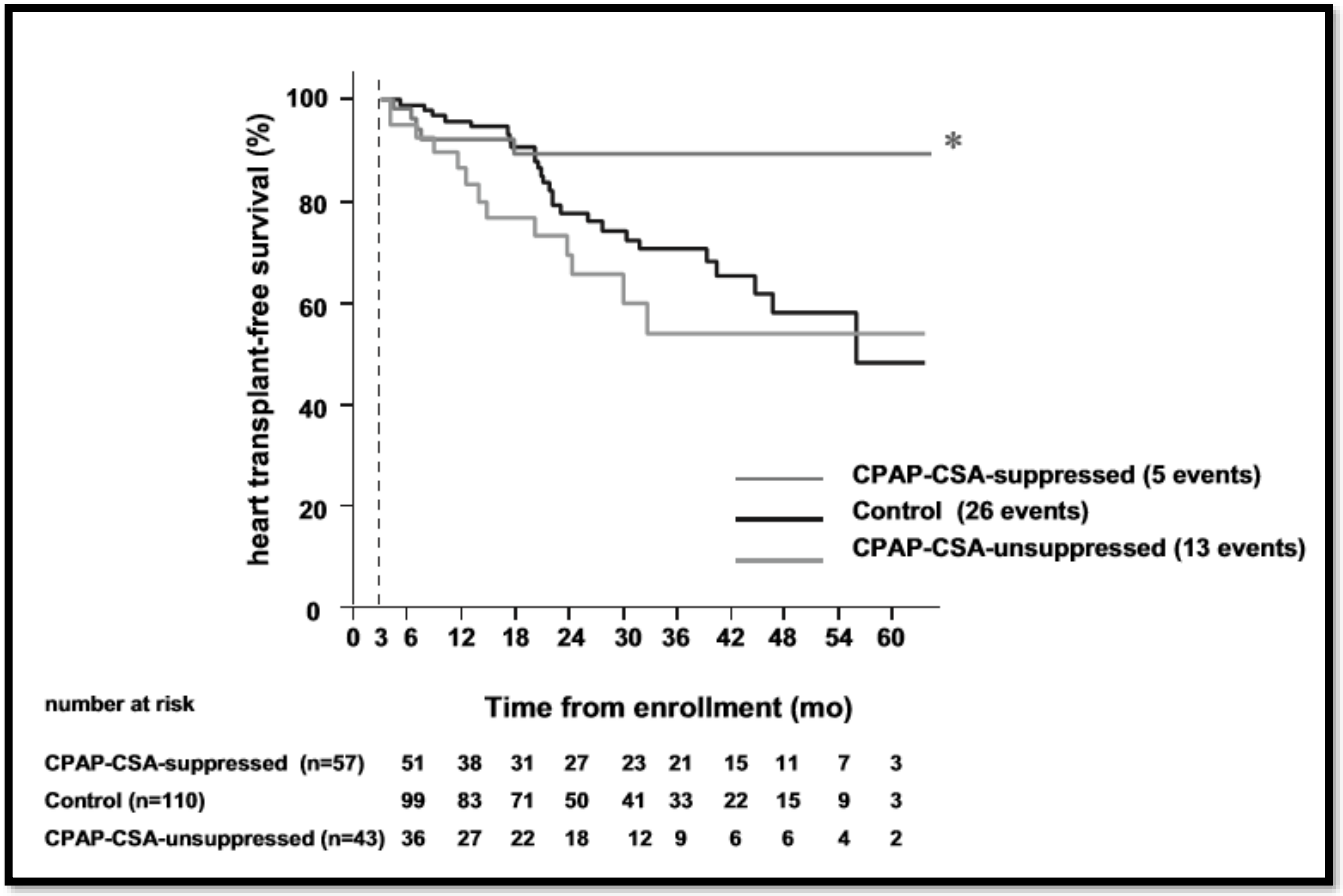



In the control group, no significant change occurred in the number of apneas and hypopneas per hour of sleep (AHI) from baseline to 3 months (from 38 [35 to 41] to 36 [33 to 40] per hour of sleep). In both the CPAP-CSA–suppressed and CPAP-CSA–unsuppressed groups, the AHI was reduced from baseline to 3 months (from 34 [30 to 37] to 6 [5 to 7], P0.001, and from 47 [42 to 52] to 35 [31 to 39] per hour of sleep, respectively; P0.001), and these reductions were significantly greater than in the control group (P0.001 and P0.002, respectively)




In the CPAP-CSA– unsuppressed group, LVEF did not change significantly from baseline to 3 months (mean change: 0.3% [-1.0% to 1.6%]), and this change did not differ significantly from that in the control group (0.4% [-0.6% to 1.5%]). In contrast, in the CPAP-CSA–suppressed group, LVEF increased significantly from baseline to 3 months (3.6% [2.1% to 5.1%], P0.001), and this increase was significantly greater than in both the control group (P0.001) and the CPAP-CSA–unsuppressed group (P=0.006)

# Kaplan-Meier survival plots




Compared with the control group, the CPAP-CSA–suppressed group had significantly improved heart transplant–free survival (*unadjusted P=0.043), whereas the CPAP-CSA–unsuppressed group did not (unadjusted P=0.260)

# AASM Recommendation

- CPAP therapy targeted to normalize the apnea hypopnea index (AHI) is indicated for the initial treatment of CSAS related to CHF. (STANDARD)
- An alternate treatment option should be considered in the absence of adequate control of CSAS related to CHF with CPAP

# Bilevel positive airway pressure (BPAP)

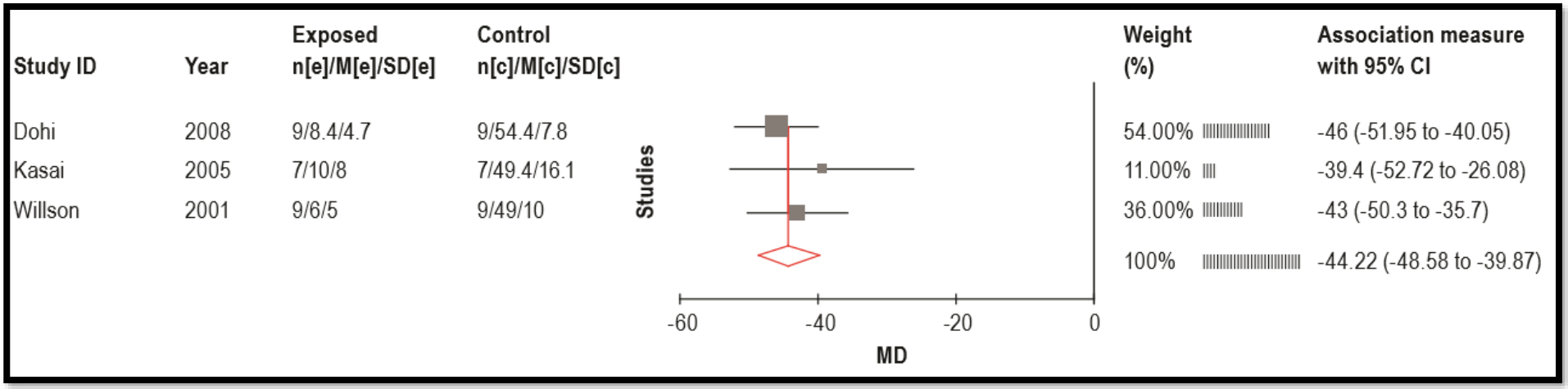
- BPAP may be used in patients who require high PAP level or as a pressure-support ventilatory method to augment alveolar ventilation
- BPAP, in the spontaneous mode, may precipitate periodic breathing and central apnea and has been used experimentally for this purpose in sleep research laboratories
- BPAP effects may be specific to the mode (spontaneous [S] or spontaneous-timed [ST] mode) or to the level of pressure support

# BPAP-S

- There is single small RCT of 10 patients on BPAP-S with standard medical therapy vs. 11 patients on standard medical therapy alone
- The change in LVEF from baseline at 3 months was reported to be +20.3% ± 8.2% with BPAP-S versus +3.2% ± 10.1% with standard medical therapy alone
- The 1 night change in AHI was 28.3 ± 12.3/h at baseline to 5.2 ± 3.8 after BPAP-S
- The patients were followed for a mean of 31.0 ± 2.3 months, and BPAP-S appeared to improve survival (10/10 patients using BPAP-S versus 7/11 controls survived)

Noda A et al, Chest 2007;131

# Meta-analysis of AHI from before-after 1-night BPAP-ST treatment trials




There were 3 studies that directly studied the effect of BPAP-ST on AHI. None of the trials had a control arm. The meta-analysis indicated an average decrease in the AHI by 44 [95% CI –40 to –49] with treatment versus baseline. All studies showed that the fixed pressure devices decreased the average AHI to less than or equal to 10

# Effect of BPAP-ST on LVEF

- Two studies reported the effects of BPAP-ST on LVEF
- Dohi et al. reported the change in LVEF versus baseline on 7 patients after 6 months of treatment as +12.7% ± 10.0%
- Kasai et al. reported in a non-randomized trial that the LVEF of the group of 7 patients receiving BPAP-ST improved 9.9% ± 8.6% over baseline versus the control group, in which the LVEF decreased by 1.4% ± 8.5%

Dohi T et al, Circ J 2008;72
Kasai T et al, Circ J 2005;69

# BPAP-ST vs CPAP

- BPAP-ST was directly compared to CPAP in a 14-day randomized crossover trial involving 16 patients with CHF(LVEF of 24 ± 7 )

| Parameter | Baseline | After CPAP | After BPAP-ST |
|---|---|---|---|
| NYHA class | 2.8 ± 0.4 | 2.0 ± 0.4 | 1.9 ± 0.5 |
| AHI | 26.7 ± 10.7 | 7.7 ± 5.6 | 6.5 ± 6.6 |

Kohnlein T et al. Eur Respir J 2002

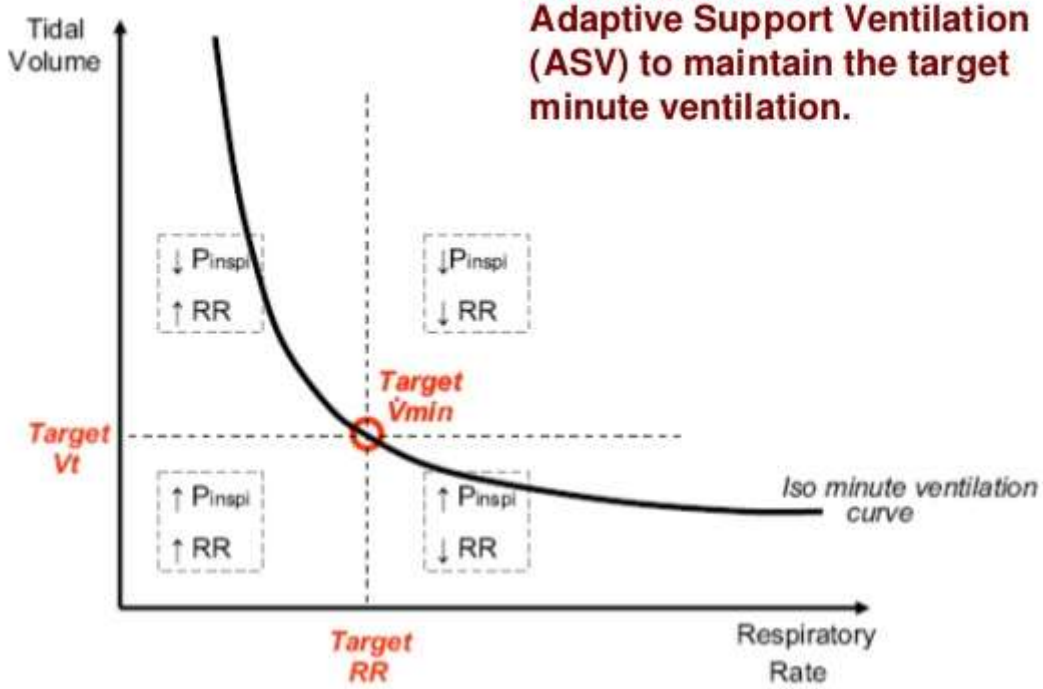
# AASM Recommendation

- BPAP therapy in a spontaneous timed (ST) mode targeted to normalize the apnea hypopnea index (AHI) may be considered for the treatment of CSAS related to CHF only if there is no response to adequate trials of CPAP and oxygen therapies. (OPTION)
  - BPAP-ST therapy offers many of the same advantages as CPAP therapy, such as low risk and easy availability but at higher cost
  - BPAP-ST may be considered only in those who fail CPAP and oxygen therapy, as these latter options have substantially more evidence supporting their use

# Adaptive Servo-Ventilation (ASV)

- ASV alleviates central sleep apnea due to CSBP by providing dynamic (breath-by-breath) adjustment of inspiratory pressure support with a back-up rate to normalize breathing patterns relative to a predetermined target
- Specifically, ASV mitigates hyperventilation and associated hypocapnia by delivering preset minute ventilation

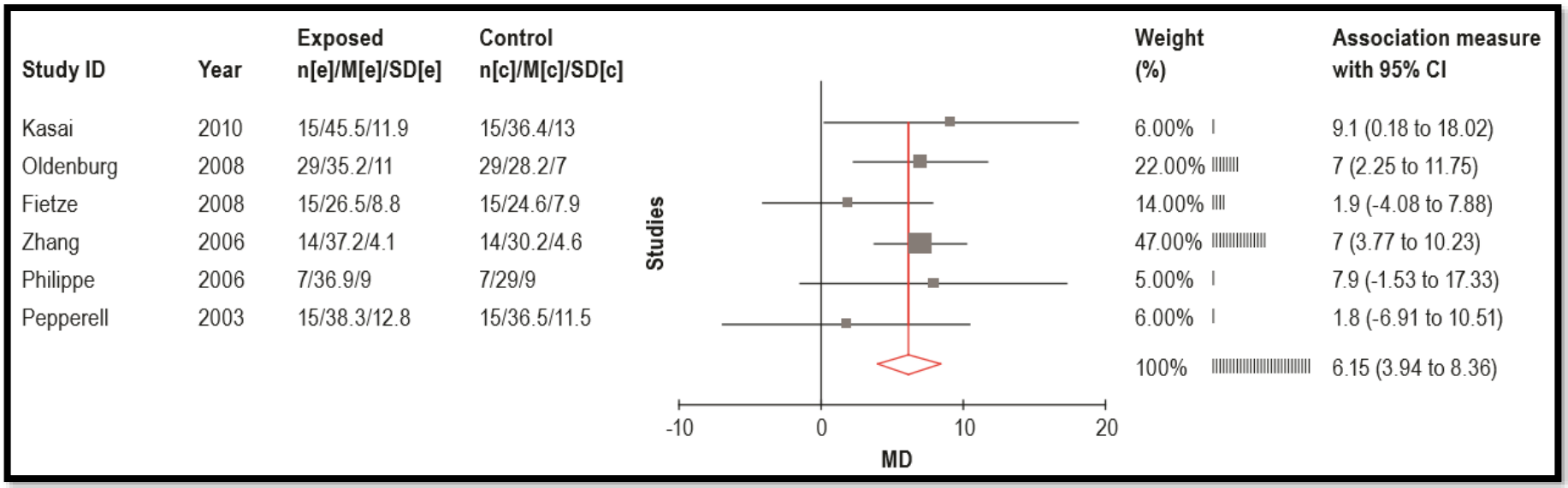
**Working principles of Adaptive Support Ventilation (ASV) to maintain the target minute ventilation.**



- Spontaneous and mandatory breaths are combined to meet the minute ventilation target
- If the patient breaths spontaneously, ventilator pressure supports breaths and encourages spontaneous breathing
- If the patient develops apnea, ventilator determines the respiratory frequency, tidal volume, pressure limit required to deliver that tidal volume, inspiratory time and I:E ratio

- As the patient begins to breath spontaneously, number of mandatory breaths decreases and the ventilator chooses a pressure support level that maintains a tidal volume sufficient to ensure alveolar ventilation
- The target is not set by the operator, but rather it is estimated by the ventilator in response to changes in respiratory-system mechanics and patient effort

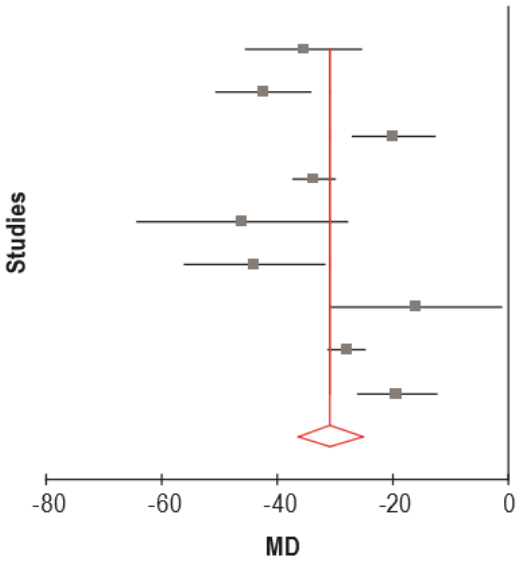
# Meta-analysis of LVEF from before-after ASV treatment trials




ASV improves LVEF by 6.2% (95% CI 3.9% to 8.4%). Two longer-term (3-6 months) studies by Philippe et al. and Kasai et al. showed a statistically significant increase in LVEF with ASV, whereas CPAP did not. Though the study by Fietze et al. showed no effect of ASV on LVEF, BPAP-ST statistically significantly increased LVEF

# Meta-analysis of AHI from before-after ASV treatment trials

| Study ID | Year | Exposed n[e]/M[e]/SD[e] | Control n[c]/M[c]/SD[c] | Weight (%) | Association measure with 95% CI |
|---|---|---|---|---|---|
| Kasai | 2010 | 15/1.9/2.1 | 15/37.4/19.5 | 11.00% | -35.5 (-45.43 to -25.57) |
| Arzt | 2008 | 14/4/3.7 | 14/46.4/15 | 12.00% | -42.4 (-50.49 to -34.31) |
| Fietze | 2008 | 15/11.1/9.9 | 15/31/10 | 13.00% | -19.9 (-27.02 to -12.78) |
| Oldenburg | 2008 | 29/3.8/4.1 | 29/37.4/9.4 | 15.00% | -33.6 (-37.33 to -29.87) |
| Morgenthaler | 2007 | 6/0/0 | 6/46/22.7 | 6.00% | -46 (-64.16 to -27.84) |
| Philippe | 2006 | 9/3/4 | 9/47/18 | 9.00% | -44 (-56.05 to -31.95) |
| Szollosi | 2006 | 10/14/12 | 10/30/20.9 | 7.00% | -16 (-30.94 to -1.06) |
| Zhang | 2006 | 14/6.5/0.8 | 14/34.5/6.1 | 15.00% | -28 (-31.22 to -24.78) |
| Pepperell | 2003 | 15/5.4/7.4 | 15/24.7/11.3 | 13.00% | -19.3 (-26.14 to -12.46) |
| | | | | 100% | -30.82 (-36.36 to -25.28) |




ASV decreases AHI by 31/h [95% CI −25 to −36] over baseline .6 of the studies showed a normalization of AHI to 5 or less. Four studies report that ASV decreases AHI by 12-23 compared to CPAP treatment.Two studies showed equivalence between ASV and BPAP-ST. One study compared ASV to oxygen and found that ASV decreased the AHI by 21 events/h compared to oxygen (a decrease of 81% vs. 19%, respectively).

# Previous recommendation

- Adaptive Servo-Ventilation (ASV) targeted to normalize the apnea-hypopnea index (AHI) is indicated for the treatment of CSAS related to CHF. (STANDARD)
  - The cost of these devices is several-fold greater than the cost of CPAP, and availability is not universal

- In a RCT, Martin R. Cowie et al. randomly assigned 1325 patients with a LVEF of 45% or less, an AHI of 15 or more events per hour, and a predominance of central events to receive guideline-based medical treatment with ASV or guideline based medical treatment alone (control)
- The primary end point in the time-to-event analysis was the first event of death from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock), or unplanned hospitalization for worsening heart failure

Martin RC et al. N Engl J Med 2015;373

| Event | Control (N=659) | | Adaptive Servo-Ventilation (N=666) | | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|---|---|
| | No. of Patients (%) | No. of Events/Yr (95% CI) | No. of Patients (%) | No. of Events/Yr (95% CI) | | |
| Primary end point† | 335 (50.8) | 0.212 (0.190–0.236) | 360 (54.1) | 0.245 (0.220–0.272) | 1.13 (0.97–1.31) | 0.10 |
| First secondary end point† | 317 (48.1) | 0.200 (0.179–0.224) | 345 (51.8) | 0.235 (0.211–0.261) | 1.15 (0.98–1.34) | 0.08 |
| Second secondary end point† | 465 (70.6) | 0.405 (0.369–0.444) | 482 (72.4) | 0.441 (0.403–0.483) | 1.07 (0.94–1.22) | 0.28 |
| Death from any cause | 193 (29.3) | 0.093 (0.081–0.107) | 232 (34.8) | 0.119 (0.104–0.135) | 1.28 (1.06–1.55) | 0.01 |
| Cardiovascular death | 158 (24.0) | 0.076 (0.065–0.089) | 199 (29.9) | 0.102 (0.088–0.117) | 1.34 (1.09–1.65) | 0.006 |
| Hospitalization for any cause | 448 (68.0) | 0.384 (0.349–0.421) | 452 (67.9) | 0.411 (0.374–0.451) | 1.05 (0.92–1.20) | 0.47 |
| Unplanned hospitalization for worsening heart failure | 272 (41.3) | 0.164 (0.145–0.185) | 287 (43.1) | 0.190 (0.169–0.214) | 1.13 (0.95–1.33) | 0.16 |
| Heart transplantation | 12 (1.8) | 0.006 (0.003–0.010) | 8 (1.2) | 0.004 (0.002–0.008) | 0.70 (0.28–1.70) | 0.43 |
| Implantation of long-term VAD | 10 (1.5) | 0.005 (0.002–0.009) | 16 (2.4) | 0.008 (0.005–0.013) | 1.67 (0.76–3.68) | 0.20 |
| Resuscitation | 19 (2.9) | 0.009 (0.006–0.014) | 25 (3.8) | 0.013 (0.008–0.019) | 1.40 (0.77–2.54) | 0.27 |
| Resuscitation for cardiac arrest | 16 (2.4) | 0.008 (0.004–0.013) | 18 (2.7) | 0.009 (0.005–0.015) | 1.19 (0.61–2.34) | 0.61 |
| Appropriate shock | 65 (9.9) | 0.033 (0.026–0.043) | 45 (6.8) | 0.024 (0.017–0.032) | 0.71 (0.48–1.04) | 0.08 |
| Noncardiovascular death | 35 (5.3) | 0.017 (0.012–0.024) | 33 (5.0) | 0.017 (0.012–0.024) | 1.00 (0.62–1.62) | 0.99 |

- The authors lay out two main possibilities for this surprising result
- First, they raise the possibility that positive airway pressure (PAP) therapy (not particularly adaptive servo-ventilation) might lead to adverse consequences on cardiac function in some patients. Early, small studies indicated that some patients with heart failure, particularly those with atrial fibrillation or low pulmonary-capillary wedge pressures, have reductions in cardiac output when PAP is applied

Kieley JL et al. Thorax 1998; 53
Liu PP et al. Am Rev Respir Dis 1992; 145

- A second possibility raised by the authors, is that some aspects of Cheyne–Stokes respiration may be beneficial
- In response to a Field Safety Notice issued by ResMed in May 2015, the AASM advised physicians to stop prescribing ASV to treat central sleep apnea in patients with symptomatic heart failure and left ventricular ejection fraction (LVEF) <45%

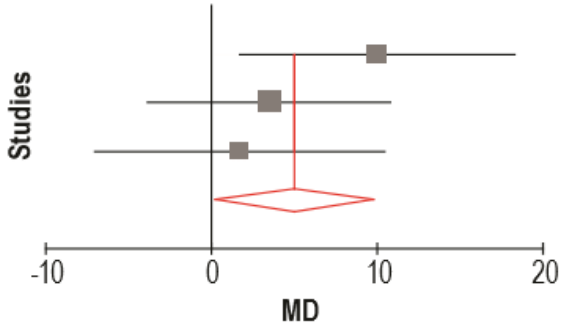
# Oxygen

- Supplemental oxygen reduces central apnea related dips in arterial $PO_2$, thereby reducing peripheral chemoreceptor stimulation
- This reduces loop gain and lessens the chance of ventilatory overshoot and dips in arterial $PCO_2$ below the apnea threshhold

Chaudhuri S et al, J Appl Physiol 2010;108

# Meta-analysis of LVEF from controlled oxygen treatment trials

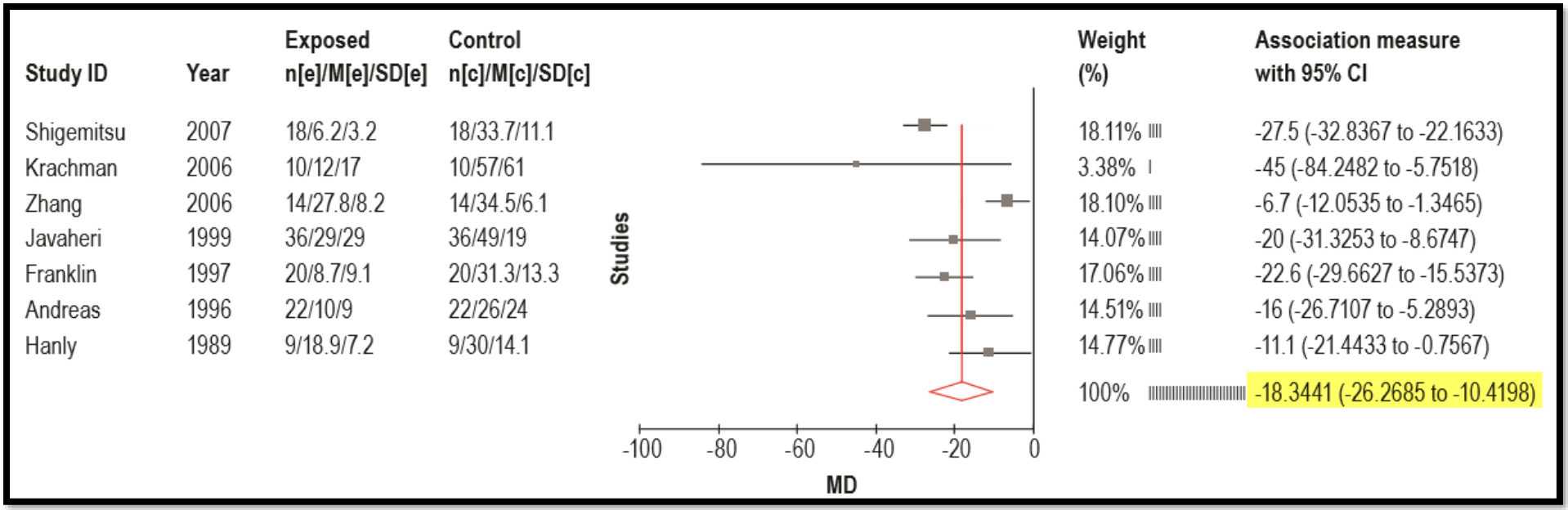
| Study ID | Year | Exposed n[e]/M[e]/SD[e] | Control n[c]/M[c]/SD[c] | Weight (%) | Association measure with 95% CI |
|---|---|---|---|---|---|
| Toyama | 2009 | 10/37/10 | 10/27/9 | 31.36% | 10 (1.6615 to 18.3385) |
| Sasayama | 2009 | 21/38.2/13.6 | 21/34.7/10.4 | 40.20% | 3.5 (-3.8225 to 10.8225) |
| Shigemitsu | 2007 | 18/46.4/14.8 | 18/44.7/11.9 | 28.44% | 1.7 (-7.0731 to 10.4731) |
| | | | | 100% | 5.0266 (0.2628 to 9.7904) |




Although none of the studies reported on mortality/transplant free survival, Sasayama et al. reported no difference in the cumulative incidence rate of cardiac events between the oxygen therapy and control groups (hazard ratio for cardiac events 0.78; 95% CI, 0.30-2.05; P = 0.619 [log-rank test])

Sasayama S et al. Circ J 2009;73:1255-62

# Meta-analysis of AHI from before-after oxygen treatment trials




Other findings from these studies include: a reduction in sympathetic nerve activity, patient symptoms (as measured by Epworth Sleepiness Scale or Visual Analogue Scale), and statistically significant improvements in sleep (decreased stage 1 sleep and arousals with increased stage 2 and slow wave sleep); however, daytime symptoms did not improve significantly

# AASM Recommendation

- Nocturnal oxygen therapy is indicated for the treatment of CSAS related to CHF. (STANDARD)
  - The universal availability of oxygen therapy coupled with the overall quality of evidence influenced the level of recommendation
  - While oxygen therapy does not confer outcome advantages over CPAP therapy in the available evidence, supplemental oxygen can be easily administered and can be given for those individuals with CSAS related to CHF who are unable to comply with CPAP therapy

# Alternate therapies for CSAS related to CHF

- There are 2 studies looking at the use of theophylline for the treatment of CHF related CSAS: 1 randomized crossover (Javaheri et al.) and 1 non-randomized treatment trial (Hu et al.)
- Both studies demonstrated statistically significant declines in the AHI (42.6 ± 15.5 to 20.8 ± 13.2 and 47 ± 21 to 18 ± 17) , and Hu et al. showed a statistically significant decrease in EEG arousals with theophylline use
- However, no statistically significant changes in sleep architecture,sleep efficiency, or LVEF were observed

Javaheri S et al, N Engl J Med 1996;335
Hu K et al, Chin Med J 2003;116

# Carvedilol

- In 2 studies,Tamura et al. reported statistically significant improvements in both LVEF (32% ± 7.4% to 45% ± 9.8%, $P < 0.001$) and AHI (34 ± 13 to 14 ± 13, $P = 0.003$) with 10-20 mg/d of the β-blocker carvedilol
- However, the mechanisms through which the improvement in the CAI is effected are not clearly delineated
- While there is some evidence that β-blockers decrease central chemosensitivity, it is likely that improvement in LVEF plays a key role in the concomitant decline seen in central respiratory events

Tamura A et al,Circ J 2009;73
Tamura A et al, Chest 2007;131

# Captopril

- Role of captopril on sleep quality in patients with mild to moderate cardiac failure was studied in an open observational study
- 12 patients with NYHA class II-III heart failure were studied at baseline. 9 of these patients were then examined at the end of 1 month of treatment with captopril 75 mg OD

Walsh JT et al. Br Heart J 1995;73:237-241

| *Variable* | *Baseline (n = 8)* | *Captopril (75 mg daily for 1 month) (n = 8)* |
|---|---|---|
| Actual sleep time (min) | 412 (29) | 342 (22) |
| Stages 1 and 2 (% actual sleep) | 61 (8) | 48 (6)* |
| Stages 3 and 4 (% actual sleep) | 25 (6) | 31 (5)* |
| REM sleep (% actual sleep) | 14 (2) | 21 (5)* |
| No of arousals | 33 (5) | 18 (3)** |
| Desaturation events | 171 (60) | 73 (37)* |
| Apnoea/hypopnoea | 242 (59) | 118 (30)* |
| Apnoea/hypopnoea/h | 35 (7) | 20 (5)* |
| Minimum oxygen saturation (%) | 83 (3) | 85 (4) |

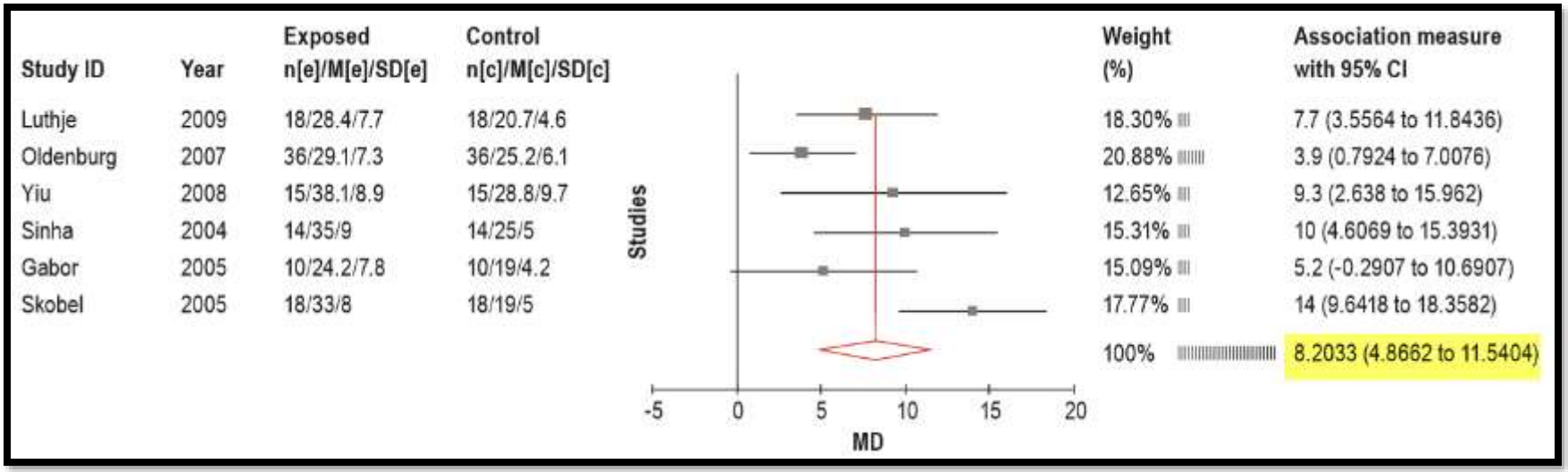
Values are means (SEM). *P < 0-05; **P < 0-01 *v* baseline.
REM, rapid eye movement.

- Overall, the use of β-blockers and ACE inhibitors has become part of the standard regimen for the treatment of CHF
- So, while the previous studies provided data showing improvement in central respiratory events with the use of these medications, it remains difficult to confidently state that these agents independently treat CSAS that is associated with CHF
- This further highlights that optimization of CHF therapy in this setting is essential

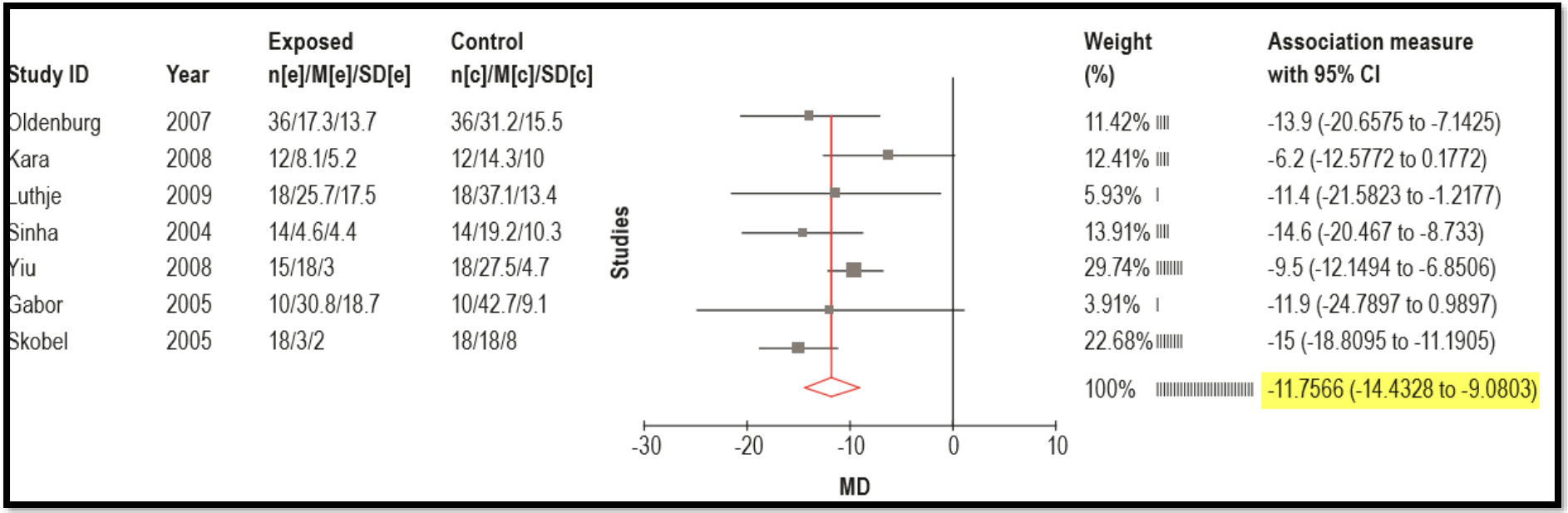
# Cardiac Interventions and CSAS

- Cardiac resynchronization therapy (CRT) involves simultaneous pacing of one or both ventricles in patients with bundle branch blocks
- Ventricular dyssynchrony in patients with CHF can further impair cardiac pump function of an already failing ventricle. CRT may improve pump performance and reverse the deleterious process of ventricular remodeling

# Meta-analysis of LVEF from CRT treatment trials



# Meta-analysis of AHI from CRT treatment trials



# Atrial overdrive pacing

- Atrial overdrive pacing (AOP) paces the atria at a higher rate, usually 15-20 beats above the baseline heart rate
- AOP helps CSAS probably by increasing cardiac output, decreasing pulmonary venous congestion, and shortening the circulation time
- In the second part of Lüthje's study, 30 patients were studied in a randomized crossover manner for 1 night. There was no statistically significant improvement with the addition of AOP to CRT (AHI 25.7 ± 17.5 vs. 23.7 ± 17.9, P = 0.07)

Luthje L et al. Eur J Heart Fail 2009;11

# Cardiac transplantation

- 13 participants with CHF + CSAS and 9 subjects with CHF but without CSAS underwent cardiac transplant
- In participants with CSAS, the AHI dropped from 28 ± 15 to 7 ± 6. Six patients were effectively cured (AHI < 5), CSAS persisted (AHI = 12.3 ± 0.9) in 3 patients, and 4 subjects developed OSA
- No one in the control group (those without CSAS) developed OSA after heart transplant

Mansfield D et al. Chest 2003;124

# CSAS Due to Medical Condition Not Cheyne Stokes: ESRD

- In a non-randomized study, Kumagai et al. reported on the effect of oxygen in 11 peritoneal dialysis patients with sleep apnea syndrome
- The nocturnal average oxygen saturation and minimum nocturnal oxygen saturation improved significantly
- The AHI decreased from 31.1 ± 8.8 to 12.7 ± 8.5/h, and the central apnea index decreased from 4.0 ± 4.0 to 0.8 ± 1.2/h with oxygen
- The authors note that the greatest effect of oxygen was on central apneas and hypopneas with little effect on obstructive apneas

Kumagai T et al, Clin Nephrol 2008;70

- In a study, Jean et al.reported the effect of bicarbonate versus acetate buffer during hemodialysis on 10 patients
- Acetate, the buffer, favors intradialytic hypoxemia through hypoventilation and ventilation-perfusion changes
- Fewer central apneas were observed with the bicarbonate buffer compared with acetate buffer (3 [range, 0-15] on bicarbonate and 33 [range, 0-180] on acetate)
- The central apnea index decreased from 5.5 to 0.6/h on bicarbonate. Hypopneas were also significantly reduced with bicarbonate (19 vs. 13 per night)

Jean G et al, Nephron 1995;71

- In a non-randomized crossover study, Hanly and Pierratos compared nocturnal hemodialysis to conventional hemodialysis in 7 patients with chronic renal failure with sleep disordered breathing events that were an equal distribution of central, mixed, and obstructive apneas
- After a treatment period of 6-15 months, the central apnea hypopnea index compared to baseline values was lower with nocturnal dialysis (4 ± 2) vs. conventional hemodialysis (24 ± 27)

Hanly P. N Engl J Med 2001;344

# AASM Recommendation

- The following possible treatment options for CSAS related to end stage renal disease may be considered: CPAP, supplemental oxygen, bicarbonate buffer use during dialysis, and nocturnal dialysis. (OPTION)
  - Despite the very low level of evidence, it is clear that bicarbonate buffer is preferable during hemodialysis in these patients

# CSAS Due to High-Altitude Periodic Breathing

- Periodic breathing during sleep results during the acclimatization period after rapid ascent to high altitudes
- A randomised, double-blind, placebo-controlled study was conducted to evaluate the effects of theophylline and acetazolamide in the treatment of sleep-disordered breathing (SDB) after fast ascent to high altitude (3,454 m)
- Theophylline was found to be equally effective compared with acetazolamide in normalizing high-altitude periodic breathing (median AHI on the first night at altitude for placebo was 16.2 [range 3-92], acetazolamide was 2.5 [0-11], and theophylline was 4.2 [0-19])

Fischer R et al, Eur Respir J 2004;23

- Additionally, only acetazolamide significantly improved basal oxyhemoglobin saturation during sleep (86.2% ± 1.7% versus 81.0% ± 3.0%)
- While no major side effects were noted, 60% of the subjects on acetazolamide developed paresthesias in their hands and feet and impaired taste
- Of the subjects on theophylline, 70% reported heart palpitations

- In a double-blinded, randomized, cross-over trial performed in Thirty-three healthy volunteers, participants took 10 mg of temazepam and placebo in random order on two successive nights soon after arrival at 5000 m, following a 17-day trek from 410 m
- Overnight SaO(2) and body movements, and next-day reaction time, maintenance of wakefulness and cognition were assessed

Nickol A et al, J Sleep Res 2006;15

- Compared with placebo, temazepam resulted in a reduction in periodic breathing from a median (range) of 16 (0-81.3)% of the night to 9.4 (0-79.6)% (P = 0.016, Wilcoxon's signed-rank test), associated with a small but significant decrease in mean nocturnal SaO(2) from 78 (65-84)% to 76 (64-83)% (P = 0.013)
- Temazepam had no adverse effect on next-day reaction time [241 (201-380) ms postplacebo and 242 (204-386) ms post-temazepam], maintenance of wakefulness (seven trekkers failed to maintain 40 min of wakefulness postplacebo, and four post-temazepam), cognition or acute mountain sickness

# AASM Recommendation

- The level of evidence is very low regarding use of a particular pharmacological agent to prevent CSAS related to high altitude and precludes the formation of a recommendation at this time
  - These medications should be used only for a short period of time due to the nature of the disorder

# CSAS due to Drug or Substance

- Limited data available
- A small non-randomized study addressed the treatment of patients on opioids (120-420 mg/d) for chronic pain who had developed CSAS and were non-responsive to CPAP
- Bilevel PAP therapy for 6 months in 4 patients decreased the AHI from 60.2 ± 30.9 at baseline to 16.6 ± 12.3. Central apneas were eliminated in 3 of the 4 patients
- In addition, the ESS scores improved, there was correction of nocturnal hypoxemia, and sleep fragmentation was reduced

Alattar M et al, Sleep Breath 2009;13

- In a study by Allam et al., use of ASV dramatically improved the AHI to a mean of 5 events per hour (range, 1 to 11) vs baseline(48 events/hour) and vs CPAP(31 events/hour) ($p < 0.0001$)
- From the reported data, only 5 patients on opioids were included in the results

Allam J et al, Chest 2007;132

- In another small non-randomized trial, Javaheri et al. reported that ASV improved sleep disordered breathing better than CPAP in 5 patients on chronic opioid treatment (252 ± 150 mg/d)

| Parameter | Baseline | CPAP | ASV |
|---|---|---|---|
| AHI | 70 ± 19 | 55 ± 25 | 20 ± 18 |
| CAI | 26 ± 27 | 37± 30 | 0 ± 0 |

Javaheri S et al, J Clin Sleep Med 2008;4

# AASM Recommendation

- The amount of evidence is very low with respect to therapy for patients with CSAS associated with opioid use and precludes the formation of a recommendation
- Assessment for discontinuation of opioid use and substitution of other forms of pain relief seems prudent

# Primary CSAS

- There is limited evidence specifically addressing therapeutic interventions for primary CSAS
- These studies reported on different treatments including supplemental carbon dioxide, acetazolamide, zolpidem, triazolam, CPAP, bilevel positive airway pressure in a spontaneous-timed mode (BPAP-ST), or ASV

- The literature on the use of PAP therapy (CPAP, BPAP-ST, ASV) for the treatment of primary CSAS is very limited

PAP therapy can be considered for the treatment of primary CSAS

respiratory events
  - (2) it typically does not confer significant risks
  - (3) it is readily available in most centers

# Acetazolamide

- 2 non-randomized treatment studies reported on the use of acetazolamide for primary CSAS
- One (DeBacker et al) looked at low-dose (250 mg/day) acetazolamide use, while the other (White et al) employed high-dose acetazolamide (1000 mg/day) therapy
- Low dose acetazolamide was found to significantly decrease the AHI (from 37.2 ± 23.2 to 12.8 ± 10.8) in 14 patients at 1-month follow-up
- The central apnea index significantly decreased (from 54 ± 29 to 12 ± 20) in 6 patients after 1 week of therapy with high-dose use

DeBacker W et al, Am J Respir Crit Care Med 1995

White D et al, Arch Intern Med 1982

- Given the low overall quality of evidence and the potential for side effects including paresthesias, tinnitus, gastrointestinal symptoms, metabolic acidosis, electrolyte imbalance, and drowsiness, the use of acetazolamide for the treatment of primary CSAS received an OPTION level recommendation

# Zolpidem

- In a non-randomized treatment trial, Quadri et al. reported that zolpidem decreased AHI from 30.0 ± 18.1 to 13.5 ± 13.3 (P = 0.0001) over an average of 9 weeks of treatment in 20 patients. Zolpidem also decreased the central apnea hypopnea index (CAHI) and arousals, improved sleep quality and subjective excessive daytime sleepiness, but had mixed results in terms of its effect on obstructive events
- In a randomized crossover trial, Bonnet et al. reported that triazolam decreased AHI (P = 0.05) and significantly decreased the central apnea index in 5 patients

Quadri S et al. J Clin Sleep Med 2009

Bonnet M et al. . Sleep 1990

- Due to the limited available evidence and the significant potential for adverse side effects especially respiratory depression, the use of zolpidem and triazolam in the setting of primary CSAS is not a preferable option and remains the last therapeutic option, to be considered only if the other therapeutic options listed above fail. Very close clinical follow-up must be provided to consider the use of these hypnotic agents

# Take home message

- CPAP therapy targeted to normalize the apnea-hypopnea index (AHI) is indicated for the initial treatment of CSAS related to CHF
- Nocturnal oxygen therapy is indicated for the treatment of CSAS related to CHF
- ASV should not be used to treat central sleep apnea in patients with symptomatic heart failure and left ventricular ejection fraction (LVEF) <45%

# Take home message(contd.)

- BPAP therapy in a spontaneous timed (ST) mode targeted to normalize the apnea-hypopnea index (AHI) may be considered for the treatment of CSAS related to CHF only if there is no response to adequate trials of CPAP and oxygen therapies
- Acetazolamide and theophylline have limited supporting evidence but may be considered for the treatment of CSAS related to CHF after optimization of standard medical therapy, if PAP therapy is not tolerated, and if accompanied by close clinical follow-up
- Positive airway pressure therapy may be considered for the treatment of primary CSAS