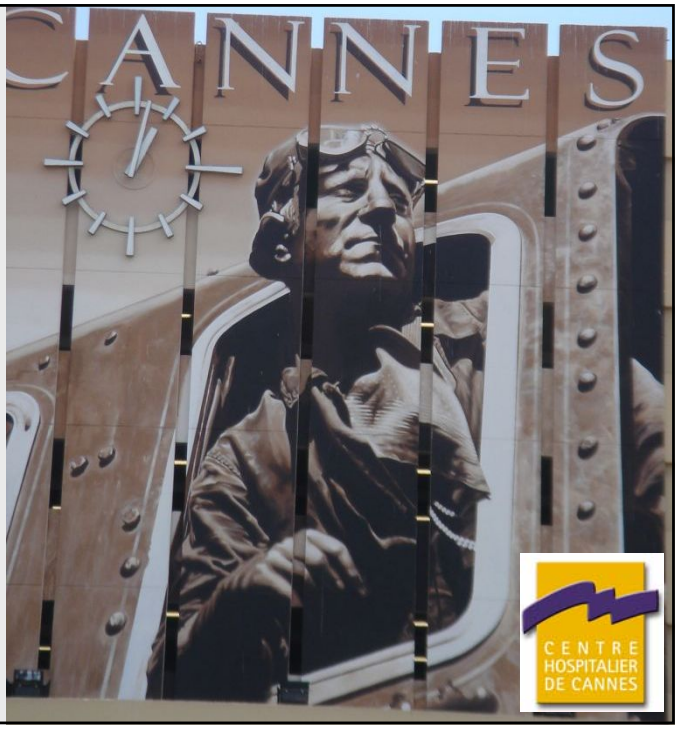
VENTILATION SERVO-ASSISTEE DANS LES APNEES CENTRALES: *UTILE ou FUTILE ?*



Rencontres Genevoises de Pneumologie 2009

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Service de Pneumologie
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APNEES CENTRALES

- Défaut ou absence de ventilation (itératif)
- Absence d'effort inspiratoire au cours des évènements
- Altération des échanges gazeux
- « Overlap » physiopathologique entre apnées obstructives et centrales
- Diagnostic différentiel parfois difficile

CENTRAL SLEEP APNEA

Manifestations

- *Hypercapnic Central Sleep Apnea*
  - . Impaired central drive ("won't breathe")
    - .. Tumors, trauma to brainstem, congenital central hypoventilation suyndrome ("Ondine curse")
    - .. Acute use of opioid-based medications
    - .. Obesity hypoventilation syndrome
  - . Impaired respiratory motor control ("can't breathe")
    - .. Neuromuscular disorders
    - .. Chest wall syndromes (kyphoscoliosis)
- *Nonhypercapnic Central Sleep Apnea*
  - . Cheyne-Stokes breathing
  - . Idiopathic Central Sleep Apnea
  - . Periodic breathing (altitude-induced breathing instability)

APNEES CENTRALES
Epidémiologie

Apnées centrales fréquentes chez le sujet sain en haute altitude

France : IMC > 30 kg/m2 (15% de la population)

Syndrome d'apnée centrale idiopathique (< 5%)

Respiration de Cheyne-Stokes : 37% des patients avec FEVG < 45%

DIAGNOSIS	HYPOVENTILATION	APNEAS or HYPOPNEAS	
		Central	Obstructive
MD	Mostly	Yes	Yes
ALS	Mostly	Yes	Rare
SCI (above C5)	Yes	Yes	Mostly
DMD	Yes	Mostly with increasing age	Mostly in young patients
MG	Yes	Mostly	No

Mostly meaning > 50%; Yes meaning a third; Rare meaning < 10%;
MD : myotonic dystrophy ; **ALS :** amyotrophic lateral sclerosis ;
SCI : spinal cord injury ;
DMD : Duchenne muscular dystrophy ; **MG :** myasthenia gravis.

Fernandez AZ et al. Ann Surg 2004; 239 : 698
Sturm R et al. Arch Intern Med 2003; 163 : 2146
Perrin C et al. Sem Respir Crit Care Med 2005; 26 : 117
Javaheri S. Int J Cardiol 2006; 106 : 21-28
Eckert DJ et al. Chest 2007; 131 : 595-607

PRISE EN CHARGE THERAPEUTIQUE
BENEFICES ESCOMPTES

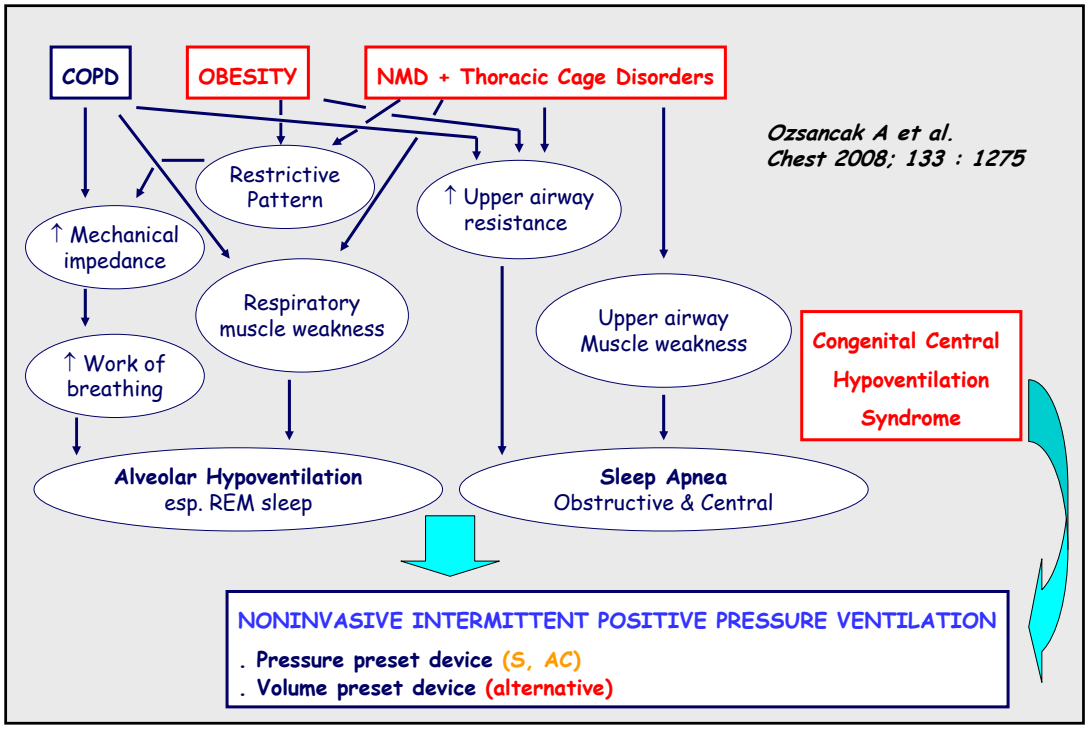
Symptômes

Fragmentation du sommeil

Hypersomnolence diurne

Morbidité cardiovasculaire

- Corriger l'hypoxie intermittente au cours du sommeil
- Améliorer la qualité du sommeil (IAH, TTS, architecture, microéveils)
- Améliorer la qualité de vie
- Diminuer les hospitalisations pour exacerbations aiguës
- Prolonger la survie



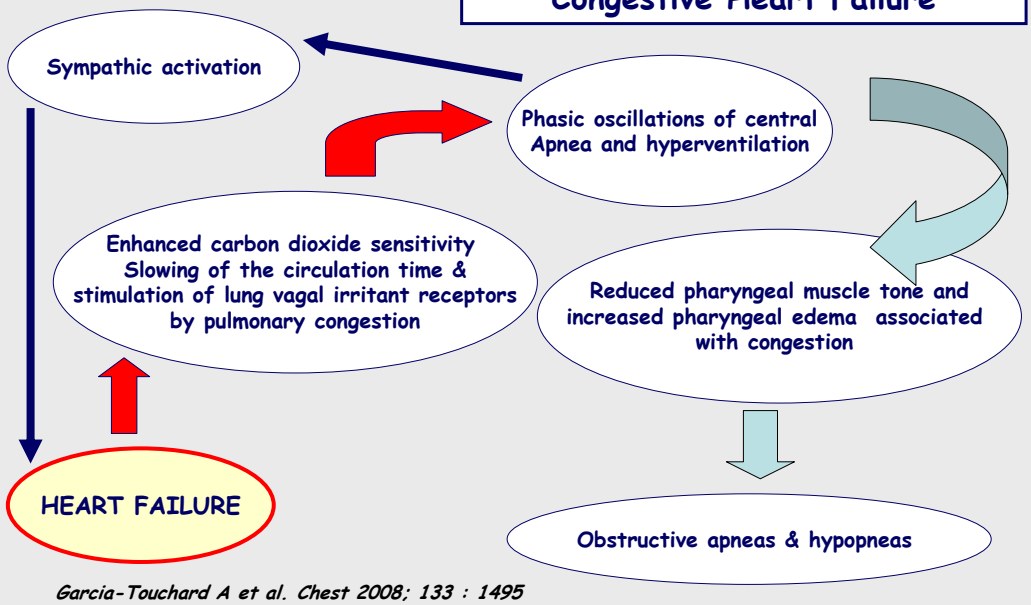
Ozsancak A et al.
Chest 2008; 133 : 1275

Idiopathic Central Sleep Apnea

CPAP	May normalize AHI in some patients	Very limited data available	Case report and 1 small short-term non-RCT
CO2; ↑dead space	Normalizes AHI	No long-term safety data	1 small short-term non-RCT
O2	Normalizes AHI	Very limited data available	1 small (2 ICSA patients) non-RCT
Atrial overdrive, pacing	Approximate ↓ AHI (60%)	Several subsequent negative study	Several, small short-term RCTs
Acetazolamide	Approximate ↓ AHI (70%)	No long-term safety data	1 small short-term non-RCT

Eckert DJ et al. Chest 2007; 131 : 595-607

CHEYNE-STOKES RESPIRATION
Congestive Heart Failure



Garcia-Touchard A et al. Chest 2008; 133 : 1495
Ozsancak A et al. Chest 2008; 133 : 1275

CHEYNE-STOKES RESPIRATION
Outcomes

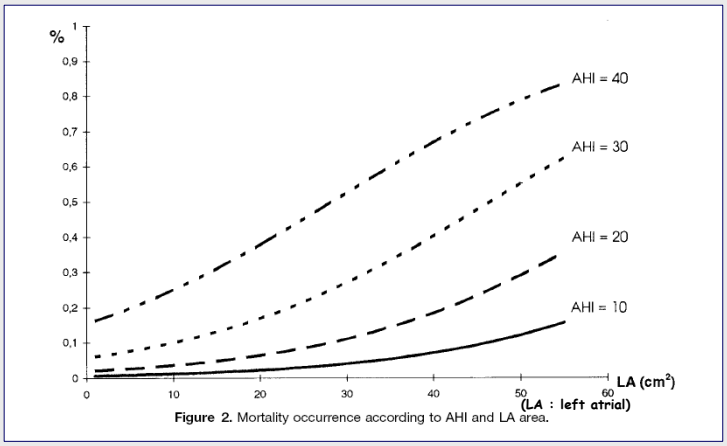


Figure 2. Mortality occurrence according to AHI and LA area.

Lanfranchi PA et al. Circulation 1999; 99 : 1435-1440

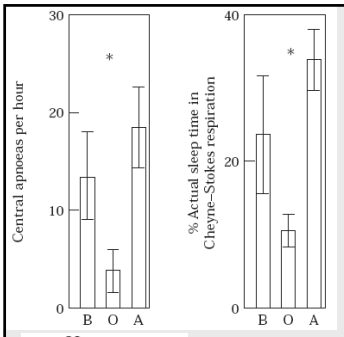
RESPIRATION DE CHEYNE-STOKES
Thérapeutiques

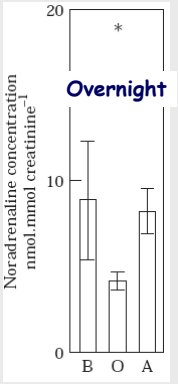
- **Optimisation du traitement médical**
  ou chirurgical de l'insuffisance cardiaque
- **Inhalation de CO2 ou majoration de l'espace mort (études de cas limitées)**
  . **Effets sur IAH discutables**
  . **Effets secondaires :**
  .. **Activation du système sympathique**
  .. **HTAP, allongement QT**
- **Theophylline**
  . **Améliore IAH**
  . **↓ désaturations en oxygène**

  } **Mécanisme ?**

  . **Réserve de sécurité : troubles du rythme cardiaque (long terme)**

Rubin AE et al. Thorax 2004; 59 : 174-176
Lorenzi-Filho G et al. Am J Respir Crit Care Med 1999; 159 : 1490-1498
Javaheri S et al. N Engl J Med 1996; 335 : 562-567





Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne–Stokes respiration

Double-blind, placebo-controlled cross-over study
n = 11, 4 weeks

Table 3 Effect of overnight oxygen therapy on symptoms in patients with heart failure and Cheyne–Stokes respiration

Test	Study period		*P*
	Air	Oxygen	
Patient symptoms			
Epworth Sleepiness Scale	10 (2·1)	9·4 (1·9)	ns
Daytime somnolence, VAS	3·6 (0·9)	4·1 (0·9)	ns
Quality of life score (max 240)	113 (10)	115 (9)	ns
Cognitive function			
Reitan trailmaking B (s)	197 (43)	196 (44)	ns
PASAT, 2 s	26 (6)	28 (6)	ns
PASAT, 4 s	43 (7)	48 (6)	ns
Four choice reaction time (s)	0·82 (0·1)	0·86 (0·1)	ns
Steer Cleer (objects hit)	69 (33)	103 (40)	ns

↑ OBSTRUCTIVE APNEA INDEX

Staniforth AD et al. Eur Heart J 1998; 19 : 922-928

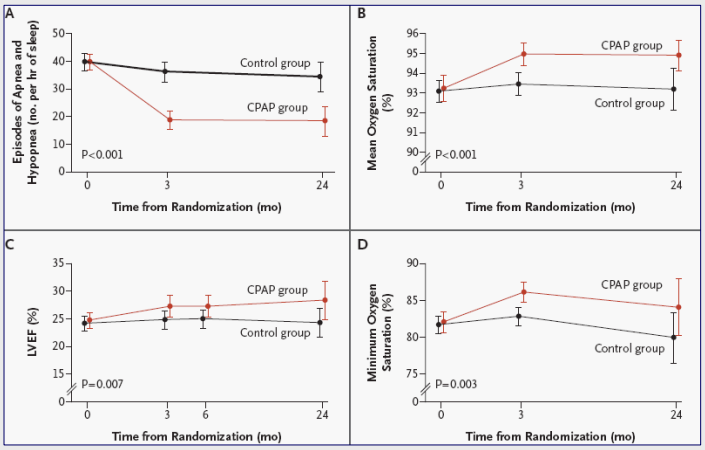
Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure RATIONALE

Continuous Positive Airway Pressure :

- May Increase dead space and CO_2 lung volume
  . CPAP may help keeping CO_2 above the apneic threshold and reduce fluctuations in $PaCO_2$
- May improve OSA
- May reduce the number of post-arousal central apneas
- May reduce cardiac afterload and preload,
  ⇒ cardiac function improvement
- May reduce interstitial edema
  thus could reduce pulmonary vagal efferent stimulation leading to reduce ventilatory drive

Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure

Randomized Controlled Trial (CPAP *versus* Control)
n = 258



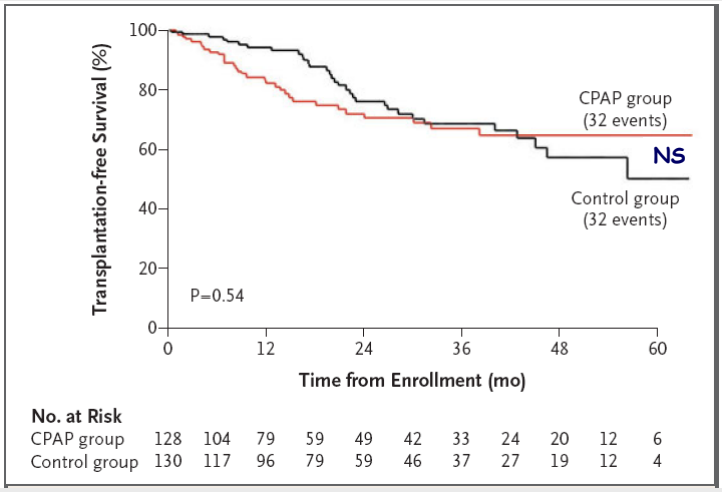
CPAP setting unmonitored (highest pressure Tolerated) 3 nights

Bradley TD et al.
N Engl J Med 2005;353:2025

↑LVEF (2.2%) : reduction in cardiac sympathetic drive, left ventricular unloading, reducer myocardial ischemia (↑SaO2)

Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure

Randomized Controlled Trial (CPAP *versus* Control)
n = 258



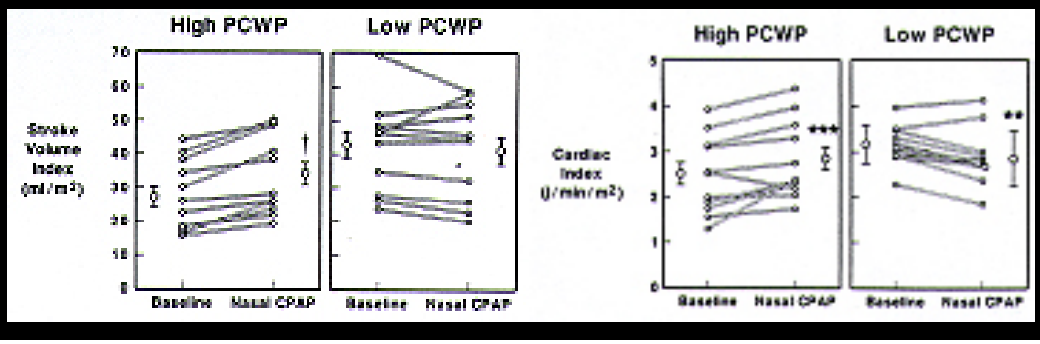
No. at Risk											
CPAP group	128	104	79	59	49	42	33	24	20	12	6
Control group	130	117	96	79	59	46	37	27	19	12	4

Bradley TD et al.
N Engl J Med 2005;353:2025

CARDIAC OUTPUT RESPONSE TO CPAP

- Congestive Heart Failure (n = 22)
  - . PCWP ≥ 12 cmH2O (n = 11)
  - . PCWP < 12 cmH2O (n = 11)
- CPAP 5 cmH2O

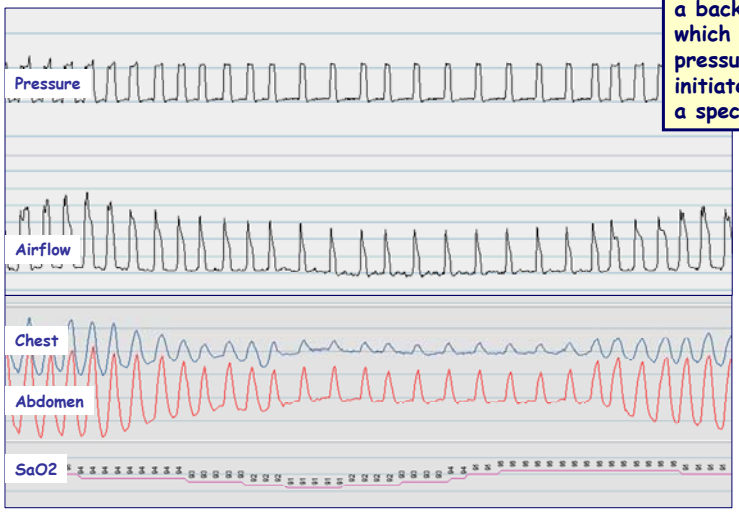
Bradley TD et al.
Am Rev Respir Dis 1992; 145 : 377-382



Bilevel Positive Airway Pressure (BLPAP) for Central Sleep Apnea and Heart Failure

RATIONALE

Bilevel ventilation can provide a backup rate, which changes to the higher pressure if the patient does not initiate a breath within a specified time.



Bilevel Ventilation For Heart Failure with Cheyne-Stokes Respiration

Köhnlein T et al. Eur Respir J 2002; 20 : 934

- AHI (NS)
  - . CPAP : 26.7 ± 10.7 → 7.7 ± 5.6
  - . Bilevel Ventilation : 26.7 ± 10.7 → 6.5 ± 6.6
- Arousal index (NS) :
  - . CPAP : 31.1 ± 10.0 → 15.7 ± 5.4
  - . Bilevel Ventilation : 31.1 ± 10.0 → 16.4 ± 6.9
- Sleep quality, daytime fatigue, circulation time : NS
- SpO2 (time spent below 90%) : NS

FIXED *low* PRESSURE LEVELS
CPAP : 8.5 cmH2O
Bilevel : IPAP 8.5 cmH2O, EPAP 3 cmH2O
(ΔIPAP/EPAP 5.5 cmH2O)

Randomized, non blinded crossover trial
CPAP *versus* Bilevel ventilation
n = 16 (14 days)

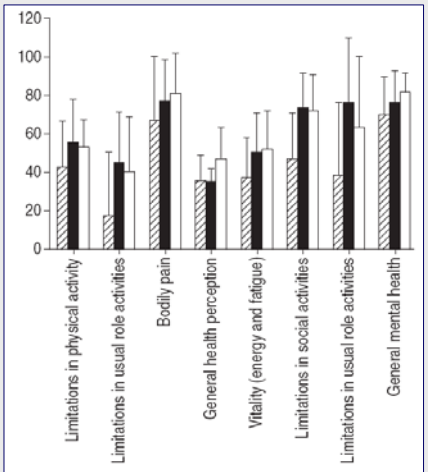
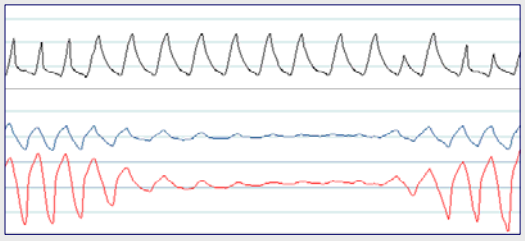


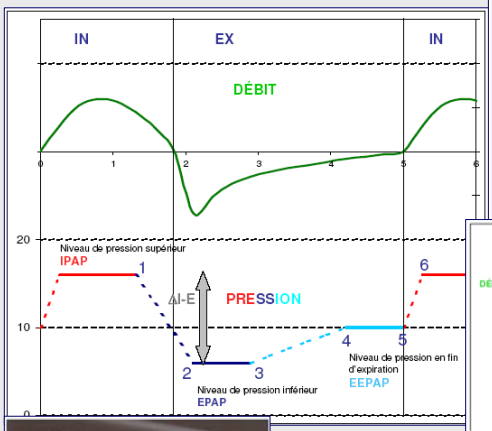
Fig. 6.–Evaluation of quality of life with the short-form health survey (SF)-36 questionnaire before (▨) and after 14 days of treatment with either continuous positive airway pressure (CPAP, ■) or bilevel positive airway pressure ventilation (BiPAP, □). The scales range 0–100 (0: bad quality of life; 100: best possible health status). All patients improved in all items after CPAP or BiPAP, but this did not reach statistical significance.

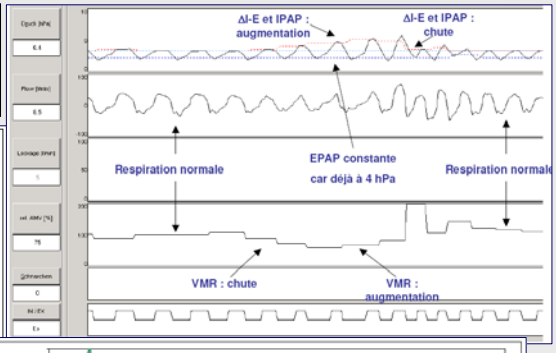
Adaptive Pressure Support Servo-Ventilation
Autoset CS2™, ResMed
ALGORITHM

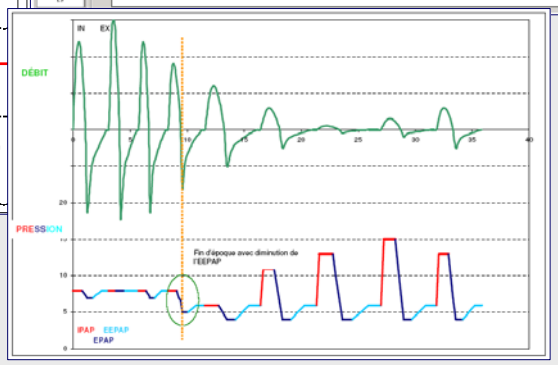
- Provides a baseline degree of ventilatory support superimposed on 5 cmH2O CPAP
- Mild waveform
- Subject's ventilation is servo-controlled with a high-gain integral controller to equal a moving target ventilation of 90% of the long-term average ventilation (time constant 3 minutes)
- IPAP default setting : 15 cmH2O reached in 12 sec
- Auto backup breath



VENTILATION SERVO-ASSISTEE SOMNOvent CR™, WEINMANN ALGORYTHME

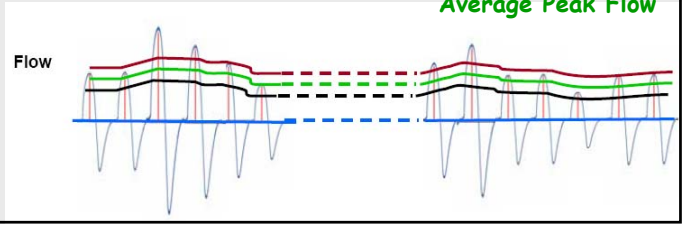






Adaptive Pressure Support Servo-Ventilation BiPAP autoSV™, PHILIPS ALGORITHM

- On a breath by breath basis peak flow is captured
- Peak flow is minitored over a moving 4 minute window
- At every point within this 4 minutes period, algorithm calculates an average peak flow
- 2 targets are calculated around this average peak flow
  - . Point above : target during SDB events
  - . Point below : target when free of SDB events
- Auto Backup Breath :
  - . delivered based on patient's spontaneous rate
  - . decreased to approximately 7-9 bpm



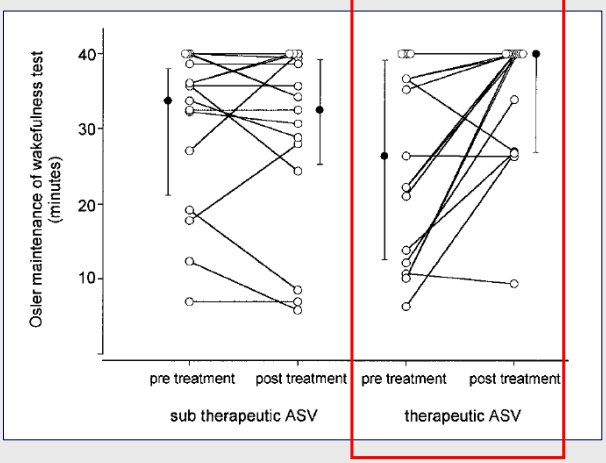
Adaptive Pressure Support Servo-Ventilation SETTING

- Initiation : at the hospital
- Patient : clinical steady state
- Facial mask
  . often, patients with Cheyne-Stokes Respiration open their mouth during hyperventilation phase
- Blood pressure checking

Adaptive Pressure Support Servo-Ventilation for Cheyne-Stokes Respiration in Heart Failure Randomized Controlled Trial

Parallel randomized double-blind trial
(ASV *versus* sham-ASV)
n = 30 (1 month)

ASV setting
IPAP 3-10 cmH2O, PEP 5 cmH2O



Self reported health status & subjective sleepiness = NS ⟷ *Trial too small & too short !*

Pepperell JCT et al. Am J Respir Crit Care Med 2003; 168 : 1109

Adaptive Pressure Support Servo-Ventilation for Cheyne-Stokes Respiration in Heart Failure Randomized Controlled Trial

TABLE 2. PLASMA B-TYPE NATRIURETIC PEPTIDE DATA FOR DAYTIME SLEEPINESS (OSLER TEST), 24-HOUR URINARY METADRENALINE, AND NORMETADRENALINE EXCRETION ARE SHOWN FOR THERAPEUTIC AND SUBTHERAPEUTIC ADAPTIVE SERVOVENTILATION AT BASELINE AND FOLLOW-UP

	Therapeutic ASV		Subtherapeutic ASV		Change with Therapeutic ASV	Change with Subtherapeutic ASV	
	Before	After	Before	After	(*n* = 15)	(*n* = 15)	p Value
Daytime sleepiness Osler, min	26.1 (3.3)	34.0 (2.3)	29.9 (2.7)	28.9 (3.2)	+7.9 (2.9)	−1.0 (1.7)	0.014
BNP, pg/ml	363 (234–875)	278 (187–493)	318 (73.2–975)	311 (113–1286)	−56.0 (−238–−16.0)	0.0 (−24.0–+71.0)	0.001
Metadrenaline, nmol/mmol creatinine	60.6 (6.1)	45.2 (4.1)	93.1 (12.2)	98.4 (12.1)	−15.4 (4.6)	+5.3 (6.8)	0.018
Metnoradrenaline, nmol/mmol creatinine	190.0 (37.6)	153.2 (20.9)	279.4 (45.1)	277.1 (41.1)	−36.6 (21.3)	−2.3 (13.7)	0.19

Definition of abbreviations: ASV = adaptive servoventilation; BNP = brain natriuretic peptide.
Note significant differences between groups for change in BNP (Mann–Whitney U test) and urinary metadrenaline excretion (unpaired *t* test).

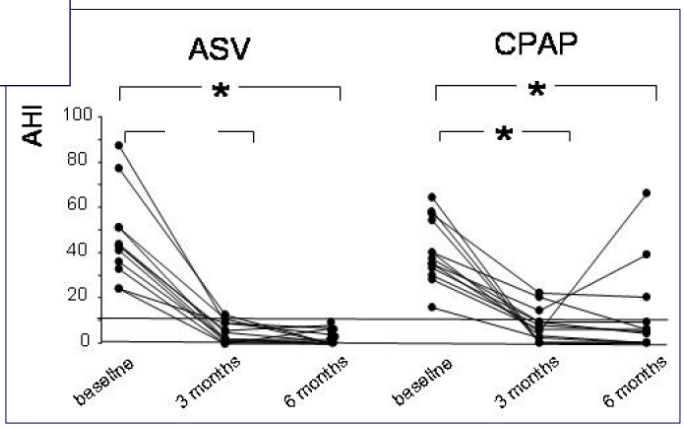
Parallel randomized double-blind trial (ASV *versus* sham-ASV) n = 30 (1 month)

ASV setting
IPAP 3-10 cmH2O, PEP 5 cmH2O

Pepperell JCT et al. Am J Respir Crit Care Med 2003; 168 : 1109

Compliance with and efficacy of adaptive servo-ventilation (ASV) versus continuous positive airway pressure (CPAP) in the treatment of Cheyne-Stokes respiration in heart failure over a six month period

Parallel randomized multi-centre trial (CPAP *versus* ASV) n = 25 (6 month)



CPAP setting
adjusted until CSA/CSR was eliminated.
CPAP : 8 cmH2O

ASV (default setting)
IPAP 3-10 cmH2O, PEP 5 cmH2O

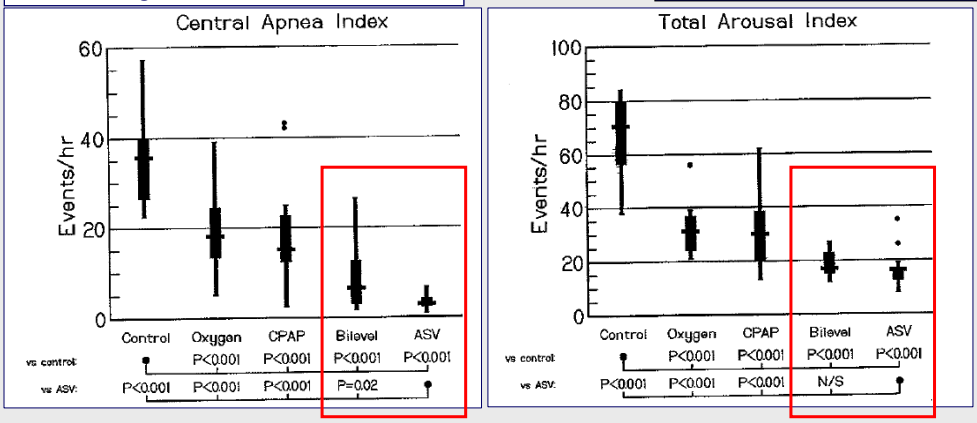
Philippe C et al. Heart 2006; 92 : 337-342

Adaptive Pressure Support Servo-Ventilation for Cheyne-Stokes Respiration in Heart Failure

CPAP & BiPAP settings
adjusted until CSA/CSR was eliminated
CPAP : 8.7 cmH2O
Bilevel : IPAP 12 cmH2O, PEP 6 cmH2O

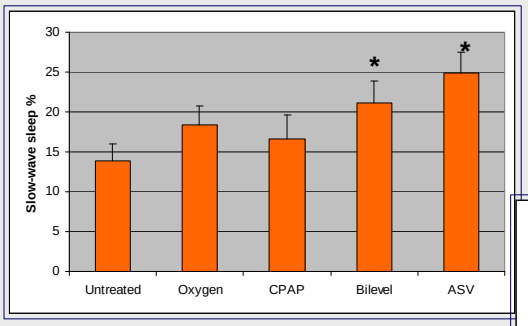
ASV : IPAP 4-10 cmH2O, PEP 4-6 cmH2O

Prospective randomized crossover trial (nasal O2, CPAP, Bilevel ventilation, ASV) n = 14 (1 night)



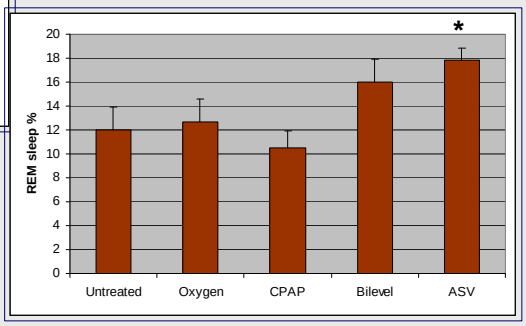
Teschler H et al. Am J Resp Crit Care Med 2001; 164 : 614

Adaptive Pressure Support Servo-Ventilation for Cheyne-Stokes Respiration in Heart Failure



CPAP & BiPAP settings
adjusted until CSA/CSR was eliminated
CPAP : 8.7 cmH2O
Bilevel : IPAP 12 cmH2O, PEP 6 cmH2O

ASV : IPAP 4-10 cmH2O, PEP 4-6 cmH2O



p value versus untreated

Teschler H et al. Am J Resp Crit Care Med 2001; 164 : 614

Adaptive servo-ventilation and deadspace: effects on central sleep apnoea

Table 2. Effect of interventions on sleep and breathing

					Post hoc (Holm)		
$n = 10$	*Control*	*ASV*	*DS*	RMANOVA	*C/ASV*	*C/DS*	*ASV/DS*
TST (h)	4.9 ± 0.4	4.7 ± 0.4	3.8 ± 0.4	0.034	ns	0.013	ns
SE (%)	72.4 ± 5.9	76.9 ± 4.0	64.2 ± 4.2	ns	–	–	–
S1 (% TST)	22.8 ± 4.4	12.6 ± 1.8	20.5 ± 2.0	0.037	0.044	ns	ns
S2 (% TST)	55.3 ± 2.6	62.4 ± 3.1	61.6 ± 4.0	ns	–	–	–
SWS (% TST)	7.9 ± 1.8	9.8 ± 1.9	6.0 ± 1.1	ns	–	–	–
REM (% TST)	13.9 ± 2.4	14.8 ± 1.8	12.1 ± 2.4	ns	–	–	–
AHI (h^{-1})	30.0 ± 6.6	14.0 ± 3.8	15.9 ± 4.7	0.013	0.017	0.034	ns
AI (h^{-1})	17.0 ± 4.5	5.5 ± 3.2	2.5 ± 1.4	0.006	0.020	0.008	ns
ArI (h^{-1})	39.6 ± 7.3	23.7 ± 2.5	38.4 ± 3.9	0.024	0.041	ns	0.041
RArI (h^{-1})	27.3 ± 8.0	11.4 ± 2.7	18.1 ± 5.8	ns	–	–	–
SArI (h^{-1})	12.3 ± 3.4	12.3 ± 2.6	22.7 ± 1.9	0.005	ns	0.009	0.008
Heart rate (sleep)	63.4 ± 2.8	61.3 ± 3.4	63.0 ± 2.5	ns	–	–	–
2% DI (h^{-1})	32.6 ± 7.8	18.6 ± 4.7	20.1 ± 7.3	0.020	0.034	0.038	ns
Mean sleep SpO_2	94.8 ± 0.8	96.2 ± 0.5	96.6 ± 0.4	0.024	ns	0.038	ns
Mean min SpO_2 (during events)	90.3 ± 1.2	93.2 ± 0.6	93.3 ± 0.6	0.005	0.021	0.007	ns
Eupnic sleep $PetCO_2$	34.8 ± 2.0	34.7 ± 2.2	37.8 ± 1.7	0.043	ns	ns	0.050

TST, total sleep time; SE, sleep efficiency; S1, stage 1; S2, stage 2; SWS, slow wave sleep; REM, rapid eye movement; AHI, apnoea-hypopnoea index; AI, apnoea index; ArI, arousal index; RArI, respiratory related arousal index; SArI, spontaneous arousal index; DI, desaturation index; ns, not significant.

Szollosi I et al. J Sleep Res 2006; 15 : 199-205

Adaptive Pressure Support Servo-Ventilation for Cheyne-Stokes Respiration in Heart Failure

TABLE 4. EFFECTS OF TREATMENT ON ARTERIALIZED CAPILLARY P_{CO_2}

	Evening	Morning	Delta	p Value
Untreated	31.9 ± 1.2 (10)	30.8 ± 0.8 (8)	−1.7 ± 1.7 (8)	0.4
Oxygen	33.9 ± 0.9 (10)	39.8 ± 0.9 (9)	6.0 ± 1.3 (9)	0.002
CPAP	31.6 ± 1.1 (10)	34.0 ± 1.5 (6)	4.2 ± 1.3 (6)	0.027
Bilevel	33.6 ± 0.8 (10)	33.6 ± 1.2 (8)	0.0 ± 1.8 (8)	1.0
ASV	31.6 ± 1.1 (10)	35.2 ± 0.8 (10)	3.6 ± 1.6 (10)	0.048
	p = 0.3	p < 0.0001	p = 0.01	

* Results are expressed as mean ± SEM (n).
† Delta = Morning − Evening where calculable. The p values on the right test H_0: Delta = 0. The p values along the bottom test H_0: no effect of treatment on evening P_{CO_2}, morning P_{CO_2} delta.

Teschler H et al. Am J Resp Crit Care Med 2001; 164 : 614

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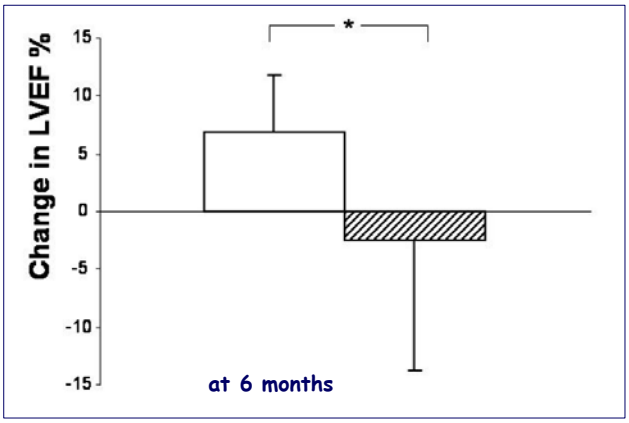
Parallel randomized multi-centre trial
(CPAP *versus* ASV)
n = 25 (6 month)

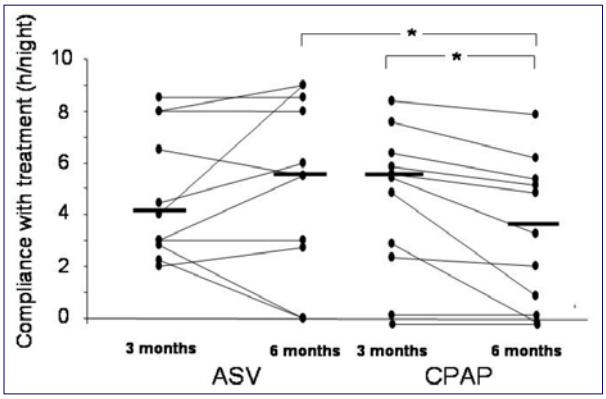
CPAP setting
adjusted until CSA/CSR was eliminated.
CPAP : 8 cmH2O

ASV (default setting)
IPAP 3-10 cmH2O, PEP 5 cmH2O



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

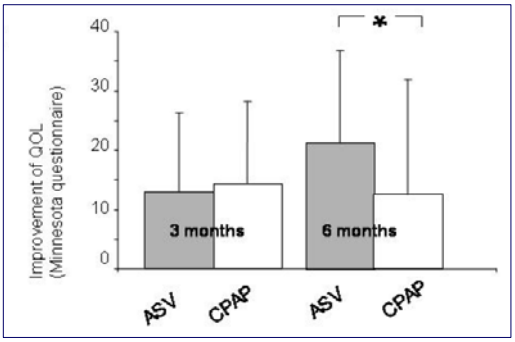
Compliance with and efficacy of adaptive servo-ventilation (ASV) versus continuous positive airway pressure (CPAP) in the treatment of Cheyne-Stokes respiration in heart failure over a six month period

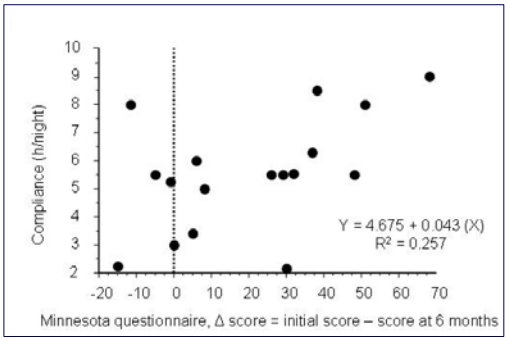


Parallel randomized multi-centre trial
(CPAP *versus* ASV)
n = 25 (6 month)

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

Compliance with and efficacy of adaptive servo-ventilation (ASV) versus continuous positive airway pressure (CPAP) in the treatment of Cheyne-Stokes respiration in heart failure over a six month period





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

Complex sleep apnea syndrome

Some patients exhibit predominantly mixed or obstructive apneas during initial diagnostic study but exhibit centrally mediated respiratory events like
Central sleep apnea / Cheyne Stokes respiration following application of positive airway pressure

Morgenthaler T et al. Sleep 2007; 30 : 468-475

Adaptive Servoventilation versus Noninvasive Positive Pressure Ventilation for Central, Mixed, and Complex Sleep Apnea Syndromes

Prospective randomized crossover trial
(NPPV *versus* ASV)
n = 21 (1 night)

	NPPV	ASV	p
AHI	6.2 ± 7.6	0.8 ± 2.4	0.002
Respiratory Arousal Index	6.4 ± 8.2	2.4 ± 4.5	0.012

Morgenthaler T et al. Sleep 2007; 30 : 468-475

Efficacy of Adaptive Servoventilation in Treatment of Complex and Central Sleep Apnea Syndromes

Retrospective
n = 100

	ASV	BPAP-S	BPAP-ST	CPAP	CPAP + O2	Diagnosis
IAH	5*	75	15*	31	10*	48

TOTAL GROUP
n = 100

Allam JS et al. Chest 2007; 132 : 1839-1846

Efficacy of Adaptive Servoventilation in Treatment of Complex and Central Sleep Apnea Syndromes

Retrospective
n = 100

	ASV	BPAP-S	BPAP-ST	CPAP	CPAP + O2	Diagnosis
IAH	4*	52	13	30	7*	30

CompSAS Group
n = 63

Allam JS et al. Chest 2007; 132 : 1839-1846

Efficacy of Adaptive Servoventilation in Treatment of Complex and Central Sleep Apnea Syndromes

Retrospective
n = 100

	ASV	BPAP-S	BPAP-ST	CPAP	CPAP + O2	Diagnosis
IAH	7*	78	11	68	31	60

CSA Group
n = 22

Allam JS et al. Chest 2007; 132 : 1839-1846

VENTILATION SERVO-ASSISTEE DANS LES APNEES CENTRALES : *utile* ou *futile ?*

RESPIRATION DE CHEYNE-STOKES
Indication documentée

- ↓ IAH
- Améliore qualité de sommeil
- Modifie les échanges gazeux de façon adaptée
- Absence d'effets hémodynamiques délétères
- Survie ? étude SERVE-HF

Bilevel Positive Airway Pressure Worsens Central Apneas During Sleep

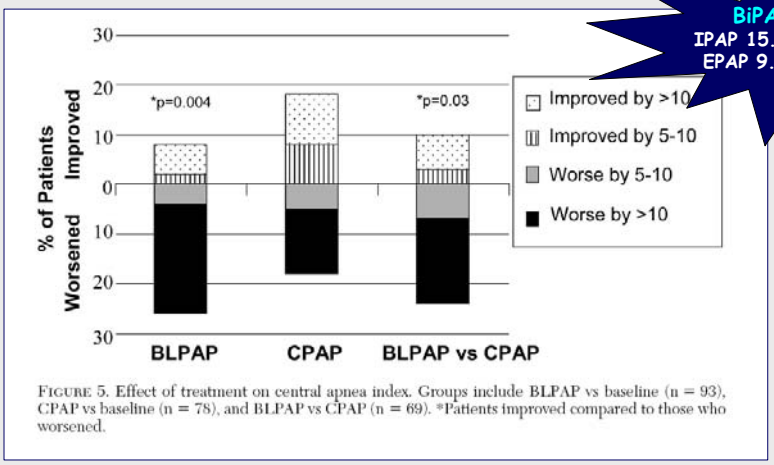


FIGURE 5. Effect of treatment on central apnea index. Groups include BLPAP vs baseline (n = 93), CPAP vs baseline (n = 78), and BLPAP vs CPAP (n = 69). *Patients improved compared to those who worsened.

BiPAP settings
IPAP 15.9 ± 4.8 cmH2O
EPAP 9.4 ± 4.4 cmH2O

ASV *versus* Bilevel
easy to set

BLPAP may ↑ VT for a given respiratory effort, contributing to instability of ventilation and making it more likely that PaCO2 wil fall below the apneic threshold

Johnson KG et al. Chest 2005; 128 : 2141

VENTILATION SERVO-ASSISTEE : *utile* ou *futile* ?

Syndrome d'apnée du sommeil COMPLEXE
Etudes complémentaires nécessaires
Place de la PPC + O2

Autres formes d'apnées centrales ?

VENTILATION SERVO-ASSISTEE : quel appareil ?