CHEYNE-STOKES, APNEAS COMPLEJAS Y CENTRALES USO DE LA VENTILACIÓN SERVO

JM Montserrat
1. Introducción

2. Apneas

3. Servo ventilación
1. Introducción

2. Apneas

3. Servo ventilación
UPPER AIRWAY PATENCY / COLLAPSE

UPPER AIRWAY FACTORS: (+)
- ANATOMIC: Obesity, retrognatia...
- COLAPSE: Shape, Tissue properties

UPPER AIRWAY MUSCLES: (-)
- Apnea

BRAIN STEM CENTERS

Cheyne Stokes Complex Apnea

Apnea
PATHOGENESIS OF CYCLICAL OSA

ANATOMICAL PREDISPOSITION TO AIRWAY CLOSURE

[↑ Passive $P_{crit}$]

- Adipose soft tissue deposition
- Compromised craniofacial structures
- ↓ Lung volume
- Airway edema
- Surface tension
- Muscle injury

SLEEP (+ sleep state discontinuity)

- Critical dependence of respiratory rhythm on $\downarrow \text{PaCO}_2$—Importance of controller/plant gains
- Tonic activity to upper airway dilator muscles, ↑ airway compliance, ↑ $P_{crit}$

UNSTABLE CENTRAL RESPIRATORY MOTOR OUTPUT

- ↓ Motor output to airway and chest wall = central apnea/hypopnea
- Passive airway narrowing/closure
- ↑ Chemoreceptor stimuli/arousal/ventilatory overshoot, hypopnea

Cyclical OSA

UPPER AIRWAY CLOSURE/APNEA

- ↑ Chemoreceptor feedback to airway/chest wall
- Arousal  airway open
- Ventilatory overshoot, hypocapnia
- ↓ Motor output to airway/chest wall = apnea/hypopnea

Dempsey et al. Pathophysiology of Sleep Apnea. Physiol Rev 2010; 47–112
UPPER AIRWAY PATENCY /COLLAPSE

UPPER AIRWAY FACTORS: (+)
ANATOMIC
  Obesity, retrognatia...
COLAPSABILYT
  Shape
  Tissue properties

UPPER AIRWAY MUSCLES (-)

BRAIN STEM CENTERS

Upper airway mechanoreceptors
  Negative pressure
  Vibration

Apnea
Kimoff et al 2009.
1. Introducción

2. Apneas

3. Servo ventilación
1. No Pueden
   - Obstructivas

2. No Quieren
   - Centrales

3. Patrón Respiratorio Irregular
   - Cheyne-Stokes, Apnea completa
LAS OBSTRUCTIVAS
Large negative intrathoracic pressures

CARDIAC OVERLOAD

Oxidative stress
Systemic inflammation
Endothelial dysfunction
Adipokines
Hypertension
Metabolic disturbances
Arteriosclerosis

Fragmented and non-restorative sleep (somnolence, cognitive...)

SaO2
Arousal
Apnea

Carples 2005. Modified
SAHS
CARDIOVASCULAR
OBESIDAD
Mice exposed to CIH and high-cholesterol diet developed atherosclerotic lesions in the aortic origin and descending aorta. 4 weeks (cross-sections of the aortic origin, using oil red O stain)

Vladimir Savransky. AJRCCM 2007
1. No Pueden
   • Obstructivas

2. No Quieren
   • Centrales

3. Patrón Respiratorio Irregular
   • Cheyne-Stokes, Apnea compleja
Electroencephalogram (measures brain activity)

Electromyelogram (measures muscle activity)

Nasal/oral airflow

Thoracic movement

Abdominal movement

Oxygen 100%

Saturation 50%

Electrocardiogram

Arousal

Apnea

Paradoxical abdominal movement with apnea

Oxyhemoglobin desaturation

Bradycardia
Normal
Airflow
Respiratory movement

Central apnea
Airflow
Respiratory movement

Mixed apnea
Airflow
Respiratory movement

Obstructive apnea
Airflow
Respiratory movement
CLASSIFICATION OF CENTRAL APNEAS

- In hypercapnic subjects:
  - neurologic or muscle deficits

- In hypocapnic or normocapnic subjects:
  - instability of the respiratory drive

- Other central apneas
Box 1. Causes of central sleep apnea

Hypercapnic central apnea
- Central congenital hypoventilation
- Arnold-Chiari malformation
- Muscular dystrophy
- Amyotrophic lateral sclerosis
- Postpolio syndrome
- Kyphoscoliosis

Nonhypercapnic central apnea
- Central apnea of sleep onset
- Periodic breathing at high altitude
- Congestive heart failure
- Acromegaly
- Hypothyroidism
- Chronic renal failure
- Idiopathic CSA
Complex sleep apnea and obesity hypoventilation syndrome opposite ends of the spectrum of OSA?

Marrone, Med Hypoth 2009

Diagram:

- OK
- Normal chemoresponsiveness
- CPAP
- OSA
- Acute CPAP
- High chemoresponsiveness
- Chronic CPAP
- Central Apneas (Complex)
- Unchanged chemoresponsiveness
- Central apneas
- Chronic CPAP
- Hypoventilation (OHS)
- Decreased (normalized) chemoresponsiveness
- OK
- Increased (normalized) chemoresponsiveness
- OK
- Unchanged chemoresponsiveness
- Hypoventilation
1. No Pueden
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3. Patrón Respiratorio Irregular
   - Cheyne-Stokes, Apnea compleja
LAS CHEYNE-STOKES
Cheyne, J.

"A case of Apoplexy, in Which the Fleshy Part of the Heart Was Converted into Fat."

Dublin Hospital Reports, 1818, II, 216.

"…For several days his breathing was irregular; it would entirely cease for a quarter of minute, then it would become perceptible, though very low, then by degrees it became heaving and quick, and then it would gradually cease again: this revolution in the state of his breathing occupied about a minute during which there were about thirty acts of respiration…"

Stokes, W.

"Observations on some Cases of permanently slow Pulse."


"…Then a very feeble, indeed barely perceptible inspiration would take place, followed by another somewhat stronger, until at length high heaving, and even violent breathing was established, which would then subside till the next period of suspension… This was frequently a quarter of minute in duration. I have little doubt that this was a case of weakened and probably fatty heart of a patient with probable cardiac asthma: 60 sec. 30 sec."
PREVALENCIA OSA EN LA INSUFICIENCIA CARDIACA
Does CSR worsen prognosis in CHF patients?

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>Number of subjects</td>
<td>16</td>
<td>36</td>
<td>62</td>
<td>66</td>
<td>78</td>
<td>133</td>
<td>88</td>
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<tr>
<td>Primary endpoints</td>
<td>Death + Tx</td>
<td>Death + Tx</td>
<td>Cardiovascular death</td>
<td>Death + Tx</td>
<td>Death</td>
<td>Death + Tx</td>
<td>Death</td>
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<tr>
<td>Male, %</td>
<td>100</td>
<td>86</td>
<td>88</td>
<td>88</td>
<td>78</td>
<td>94</td>
<td>100</td>
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<tr>
<td>Ischemic etiology, %</td>
<td>100</td>
<td>11</td>
<td>53</td>
<td>64</td>
<td>53</td>
<td>64</td>
<td>75</td>
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<tr>
<td>LVEF, %</td>
<td>23</td>
<td>20</td>
<td>23</td>
<td>22</td>
<td>20</td>
<td>23</td>
<td>24</td>
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<tr>
<td>β-Blocker, %</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>21</td>
<td>14</td>
<td>53</td>
<td>10</td>
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<tr>
<td>Sleep study</td>
<td>PSG</td>
<td>PSG</td>
<td>PSG</td>
<td>PSG</td>
<td>PSG</td>
<td>No sleep staging</td>
<td>PSG</td>
</tr>
<tr>
<td>Criteria for CSR-CSA</td>
<td>Not defined</td>
<td>CSR &gt; 20% of sleep time</td>
<td>AH1 &gt; 10</td>
<td>AH1 &gt; 15</td>
<td>AH1 &gt; 5</td>
<td>AH1 &gt; 30</td>
<td>AH1 &gt; 5</td>
</tr>
<tr>
<td>CSR-CSA risk for death and/or Tx</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Others</td>
<td>Enrolled patients with severe HF (NYHA 3 or 4)</td>
<td>Excluded patients with Afib and obesity</td>
<td>Included patients treated for CSR-CSA by CPAP, but this factor was controlled for</td>
<td>Enrolled patients from Tx unit. Included patients treated for CSR-CSA. Excluded patients with obesity</td>
<td>Included patients treated for CSR-CSA with O₂</td>
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<td></td>
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</table>
LA PERSISTENCIA DE LOS CAMBIOS QUE ACONTECEN EN LA INSUFICIENCIA CARDÍACA DAN LUGAR A UN CENTRO RESPIRATORIO INESTABLE "OPEN LOOP". ESTÍMULO – REACCIÓN

Ello hace que al cambio no sean simplemente mecánico y pueda requerir tiempo
Awake ventilation

transition

NREM

PCO₂ below apnea threshold

central apnea

Increasing PCO₂

ventilation

++

++

++

High ventilatory response to CO₂

arousal

PCO₂ above apnea threshold

Regular non-REM ventilation

Xie et al., AJRCCM 1994;150:489-95
Sin et al. Circulation, 2000
CANPAP: Survival Analysis

Heart-Transplantation-free Survival

No effect of CPAP on survival in CHF+CSA (CanPAP)

Post-hoc analysis

![Graph showing heart transplant-free survival with different groups: CPAP-CSA-suppressed (5 events), Control (26 events), CPAP-CSA-unsuppressed (13 events).]
OSA EN LA INSUFICIENCIA CARDIACA
MOTIVOS PARA CONSIDERAR SU TRATAMIENTO

HIPOXIA Y AROUSALS:
Activación simpática, inflamación

SUEÑO FRAGMENTADO:
Activación simpática, cansancio diurno p, posa somnolencia

MAYOR MORTALIDAD Y MORBILIDAD: ?

DETERIORO MAS RÁPIDO DE LA INSUF. CARDIACA: ?
1. No Pueden
   • Obstructivas

2. No Quieren
   • Centrales

3. Patrón Respiratorio Irregular
   • Cheyne-Stokes, Apnea compleja
Complex apnea is defined by the development of central apnea in the OSA patient during the initial CPAP titration.

(treatment-emergent central apnea)
COMPLEX SLEEP APNEA

At diagnosis: OSAS

During CPAP: obstructive events abolished,
But:

central apnea index ≥5 or
large amount of periodic breathing

Breakpoint: CPAP level above which respiratory periodism worsens or central apneas appear
Natural history of CompSA in OSA patients

- Retrospective analysis on over 1200 OSA patients
- Prevalence estimated at 6.5%
- AHI on CPAP decreased over time, but did not normalize in 1.5% of patients
- Risk factors for persistent CSA:
  - Severe OSA
  - High central apnea index at diagnosis
  - Use of opioids
PRO/CON DEBATE

Complex Sleep Apnea: It Really Is a Disease

Peter C. Gay, M.D.

PRO/CON DEBATE

Complex Sleep Apnea: It Isn’t Really a Disease

Atul Malhotra, M.D.; Suzie Bertsch, M.D., M.P.H.; Andrew Wellman, M.D.
### Studies on flow-triggered ASV in CHF patients with OSA+CSR

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>n</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artz et al, Chest 2008</td>
<td>Acute CPAP or BiPAP vs flow-triggered ASV</td>
<td>14 CHF</td>
<td>2 nights</td>
<td>↓ AHI, flow-triggered ASV well tolerated</td>
</tr>
<tr>
<td>Randerath et al, Sleep Med 2008</td>
<td>Flow-triggered ASV</td>
<td>10 (6 CHF)</td>
<td>8 weeks</td>
<td>↓ AHI and arousals in pts with and without CHF</td>
</tr>
<tr>
<td>Kasai et al, Circ Heart Fail 2010</td>
<td>RCT flow-triggered ASV vs CPAP</td>
<td>31 CHF</td>
<td>3 months</td>
<td>Better results in flow-triggered ASV group (↓ AHI, ↑ LVEF, QoL and compliance)</td>
</tr>
</tbody>
</table>
EPAP = 4 cm H₂O
IPAPmin = EPAP
IPAPmax = IPAPmin + 10 cm H₂O
Automatic back-up rate

Obstructive events

Central Apneas

Continued PB pattern

Final setting

Flow-triggered ASV (dynamic BiPAP): Titration

Kasai et al. Circ Heart Fail 2010; 3: 140-148
Studies on ASV in CHF patients

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</tr>
</thead>
<tbody>
<tr>
<td>Pepperell et al, 2003</td>
<td>RCT ASV therapeutic vs subtherapeutic</td>
<td>39</td>
<td>1 month</td>
<td>↓ sleepiness, AHI, BNP, urinary catechol. in therapeutic ASV group</td>
</tr>
<tr>
<td>Philippe et al, 2006</td>
<td>RCT CPAP vs ASV</td>
<td>25</td>
<td>6 months</td>
<td>↓ AHI, ↑ LVEF, better compliance and QoL in ASV group</td>
</tr>
<tr>
<td>Fietze et al, 2008</td>
<td>RCT BiPAP S/T vs ASV</td>
<td>39</td>
<td>6 weeks</td>
<td>↓ AHI, ↑ LVEF in both groups</td>
</tr>
<tr>
<td>Hastings et al, 2010</td>
<td>ASV vs no ventilatory treatment (declined ASV)</td>
<td>19</td>
<td>6 months</td>
<td>↓ AHI, ↑ LVEF, ↑ QoL, BNP= in ASV group</td>
</tr>
<tr>
<td>Koyama et al, 2010</td>
<td>ASV vs no ventilatory treatment (declined ASV)</td>
<td>17</td>
<td>4 weeks</td>
<td>↓ AHI, ↓ BNP, ↓ hsCRP in ASV group</td>
</tr>
</tbody>
</table>
Patient Characteristics

- > 90% are Male
- BMI is slightly less than average OSA patient?
- Higher incidence of ischemic heart disease or CHF Prevalence of 10-15% in OSA Patients
Polysomnographic Characteristics

May have evidence of central events on baseline PSG

Events more common in nREM sleep
Elevated Arousal Index

Possible Reduction in Central Events on future follow-up
Clinical Impact of nCPAP in “Complex Apnea”

Residual or Worsening Symptoms (Fatigue, EDS, Depression)

Secondary to Arousals/Disrupted Sleep

Higher Incidence of “CPAP Difficulty” ↑ Sympathetic Activity? of ↑ Mortality
COMPLEX SLEEP APNEA

Definition of Complex Sleep Apnea

Causes of Central Apnea Developing on CPAP Therapy

Treatment Options

Implications of the Syndrome
COMPLEX SLEEP APNEA

Definition of Complex Sleep Apnea

Causes of Central Apneea Developing on CPAP Therapy

Treatment Options

Implications of the Syndrome
Treatment Considerations in Complex Apnea

1. Increase CO2 Reserve Value
   A. ? O₂
   B. ? Induce Acidemia
   C. Increase Dead Space

2. Reduce Loop Gain
   A. Treat CHF
   B. ? Sedatives

3. Provide Back-Up
   A. Backup Rate on Therapy
Treatment Options

nCPAP with Permissive Flow Limitation

Supplemental $O_2$

Medications
- Acetazolamide
- Theophylline
- Benzodiazepines

Additional Dead Space to nCPAP

Positive Airway Pressure Gas Modulation

Adaptive Servo Ventilation (ASV)
**Implications**

1. **To OSA Patient**
   - 15% will *not* respond to nCPAP
   - Cost of Alternative Therapies may be Prohibitive

2. **To Sleep Centers**
   - Responsibility to Identify such patients and offer Treatment Modifications

3. **To Sleep Medicine Society**
   - Consider Consequences in Offering Home Studies (Non-Titrated) as well as Automated CPAP
Future Questions and Goals

Clarify Definition and Natural History of Complex Sleep Apnea

Improve Identification Process of At-Risk Patient

Improvement in Technology Utilized in making the Diagnosis

Develop Treatment Options that are Cost-Effective
1. Introducción

2. Apneas

3. Servo ventilación
Adaptive Pressure Support Servo-ventilation (APPSV)

Untreated Cheyne-Stokes Respiration

Treated Cheyne-Stokes Respiration

Teschler; AJRCCM 2001
OBJETIVO
Estabilizar la ventilación (C-S y suprimir el “open loop”)

METODOLOGÍA
Medir la ventilación previa o basal o la que supuestamente tiene el individuo

Valorar si las apneas son centrales u obstructivas

Si son obstructivas aumentar el EPAP
Si son centrales aumentar la IPAP de un modo sincronizado

Confort del paciente

RESULTADOS FINALES A ALCANZAR
Mejorar la calidad de vida, morbilidad y mortalidad
Estimar la ventilación basal del paciente
Análisis de los 1-4 minutos previos
Mantener las ventilación estimada durante el sueño
CPAP = 8 cmH₂O

Point A

Point B

ins

TIME (s)
El algoritmo ASV-CS responde a la hipopnea/apnea central

Presión de soporte ASV-CS (cm H₂O)

Flujo respiratorio al paciente

EEP + MAX PS* = 15 cm H₂O
EEP + MIN PS* = 8 cm H₂O
EEP* = 5 cm H₂O

*valores predeterminados
• EPAP\textsuperscript{MIN} = 4 \, \text{cm H}_2\text{O}, \, \text{EPAP}\textsuperscript{MAX} = 15 \, \text{cm H}_2\text{O}

• PS\textsuperscript{MIN} = 0 \, \text{cm H}_2\text{O}, \, \text{PS}\textsuperscript{MAX} = 15 \, \text{cm H}_2\text{O}

• Maximum (IPAP) pressure, P\textsuperscript{MAX} = 25 \, \text{cm H}_2\text{O}

• Back-up rate: Auto

• Bi-Flex: OFF

• Alarms: All must be disabled
Effectiveness of Different Therapies in CSA

Teschler H et. al; AJRCCM 2001
ASV vs. CPAP for CSA in HF

AHI vs. Time

C. Philippe et al., Heart 2006;92:337
Los trabajos iniciales siguen su utilidad

Hacen falta más estudios con una población más amplia dirigidos no solo a si el equipo funciona bien o no, sino si reduce la comorbilidad y mortalidad

No existen trabajos negativos Equipos sofisticados

Es imprescindible exigir a la empresas equipos robustos más que excesivamente superinteligentes
La titulación es probablemente imprescindible

No todos lo pacientes van a adaptarse inicialmente y pueden requerir varios estudios

Entreno educación a los pacientes y médicos es completamente necesaria

Los ASV no deben de ser utilizados como “black box”