Sleep apnoea and heart failure

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Disclosure

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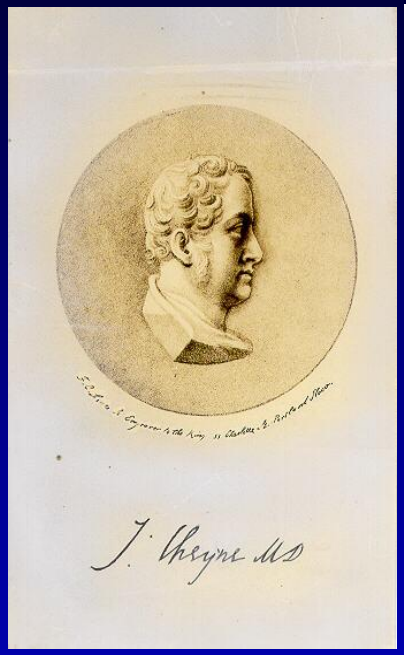
Coridea, Philips Respironics and Respicardia

Sleep apnoea in heart failure

1. Problems with nomenclature (and perception)
2. Prevalence
3. Diagnosis (in cardiology practice)
4. Pathophysiology
5. Pathophysiological and clinical consequences
6. Treatment

Sleep apnoea in heart failure
Problems with nomenclature (and perception)



. . . The only peculiarity in the last period of his illness, which lasted eight or nine days, was in the state of the respiration. For several days, his breathing was irregular; it would cease for a quarter of a 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"

John Cheyne. *A case of apoplexy, in which the fleshy part of the heart was converted into fat.* Dublin Hosp Rep. 1818:2:216-223

Sleep apnoea in heart failure
Problems with nomenclature (and perception)

Sleep Physician

Sleep disordered breathing

- **obstructive sleep apnoea**
- **central sleep apnoea**

Nomenclature accepted

Prevalent and relevant for

M&M and QoL

Target for intervention

How often you investigate whether your HF patient demonstrates sleep disordered breathing (SDB) ?

1. Rarely, SDB are clinically not really relevant
2. If he/she gives me a history of snoring
3. Tend to forget about;

typically, when I return from HF meetings

4. I regularly screen for SDB

Sleep apnoea in heart failure
Problems with nomenclature (and perception)

Cardiologist

Prevalent in obese & HTN pts

Snoring problem

Affecting QoL

Sleep Physician

Sleep disordered breathing

- **obstructive sleep apnoea**
- **central sleep apnoea**

Nomenclature accepted

Prevalent and relevant for M&M and QoL

Target for intervention

Breathing abnormality

- Cheyne-Stokes respiration
- During sleep (also at rest)

Nomenclature accepted ?

Prevalent and relevant for M&M and QoL

Target for intervention ?

Heart Failure Specialist

Sleep apnoea in heart failure
Problems with nomenclature (and perception)

- **Obstructive sleep apnoea**

  episodes of complete upper airway obstruction; prevalent in non-HF pts;

  apnoea and hypoxia & arousals from sleep

  CV consequences: hypertension, arrhythmias, myocardial ischaemia

- **Central sleep apnoea**

  temporary withdrawal of central respiratory drive

  more specific and prevalent in HF

  complex (unclear) pathophysiology; ominous consequences;

  emerging target for intervention

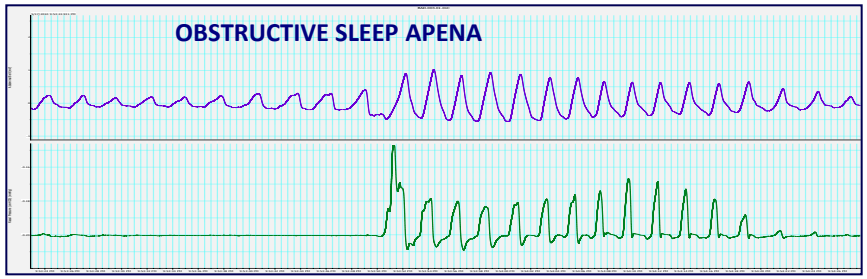
Sleep apnoea in heart failure
Problems with nomenclature (and perception)

- **Obstructive sleep apnoea**

  episodes of complete upper airway

  apnoea and hypoxia & arousals fro

  CV consequences: hypertension, a

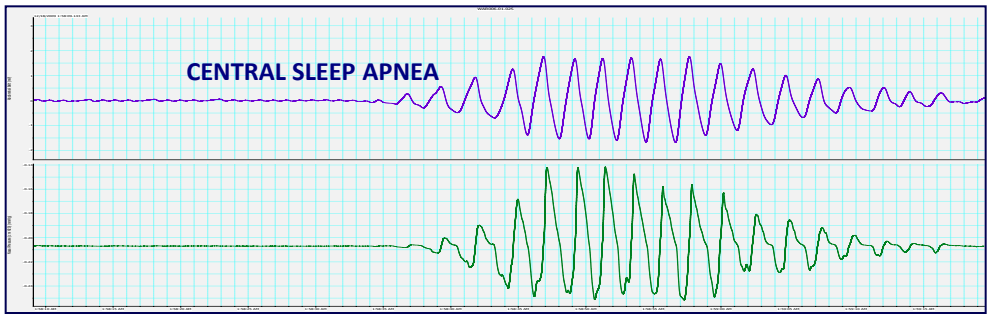


Abdominal and chest movement without airflow indicates obstructive apnea

- **Central sleep apnoea**

ory drive

nous consequences;



Lack of abdominal and chest movement indicates central apnea

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Prevalence of sleep apnea in patients with HFrEF

Country [year] Author	N	AHI ≥ 15/h	CSA	OSA	β-blockers
*USA [2006] Javaheri	100	49%	37%	12%	10%
USA [2008] MacDonald	108	61%	31%	30%	82%
*Canada [2007] Wang	287	47%	21%	26%	80%
*UK [2007] Vazir	55	53%	38%	15%	78%
Germany [2007] Oldenburg	700	52%	33%	19%	85%
*Germany [2009] Hagenah	50	64%	44%	20%	100%
*Germany [2010] Jilek	273	64%	50%	14%	88%
*Portugal [2010] Ferreira	103	46%	NA	NA	90%
Total	1676	54%	34%	20%	81%

Krawczyk M et al. Cardiol J 2013

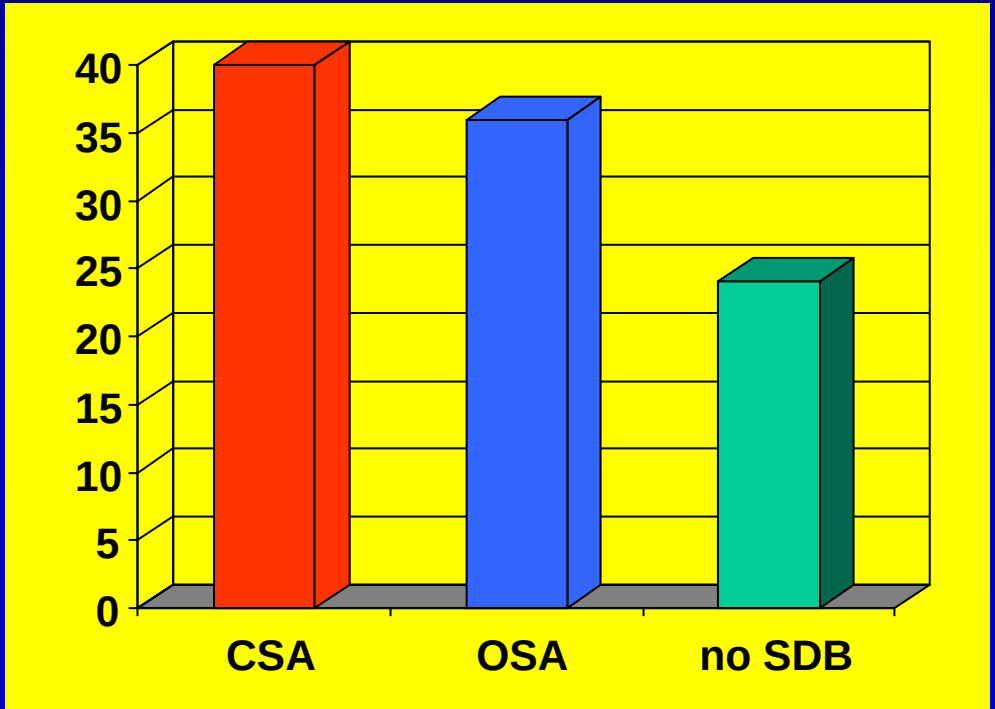
Sleep-disordered breathing in patients with symptomatic heart failure
A contemporary study of prevalence in and characteristics of 700 patients

Olaf Oldenburg [a,*], Barbara Lamp [a], Lothar Faber [a], Helmut Teschler [b], Dieter Horstkotte [a], Volker Töpfer [a]

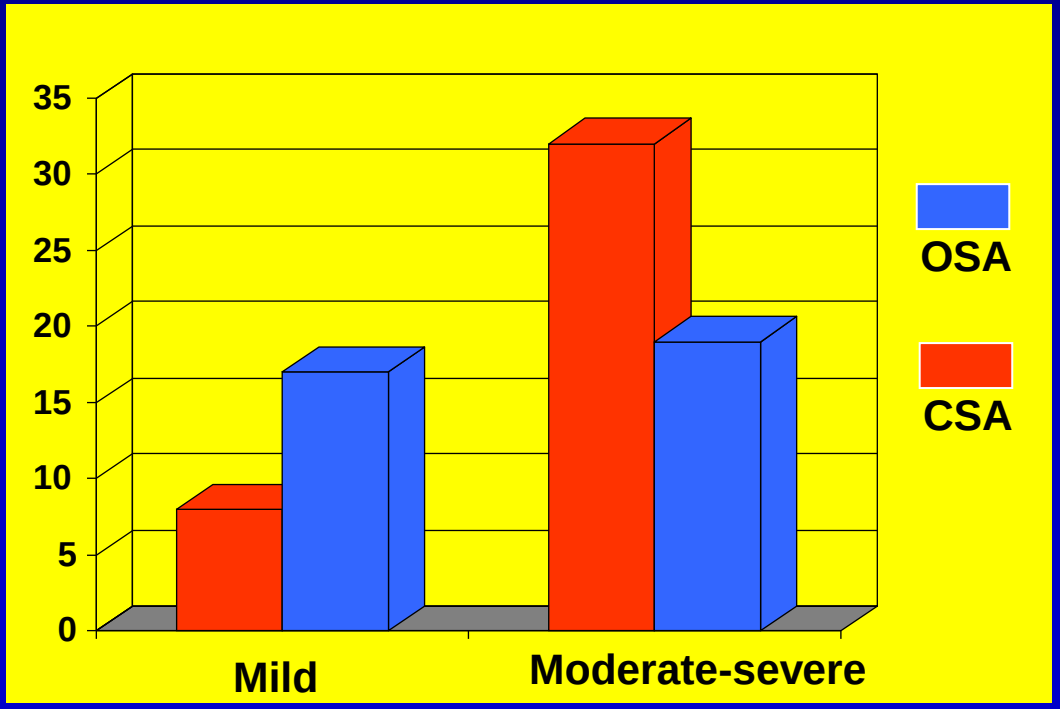
European Journal of Heart Failure 2007

- 700 CHF pts, 561 men, age: 65 yrs
- NYHA class – 2.7, LVEF – 28%, peakVO2 – 14.4 ml/kg/min
- Therapy: 95% - ACEi/ARB, 85% - beta-blocker, 90% - diuretics
- Sleep studies with cardiorespiratory polygraphy: nasal air flow, chest and abdominal effort, pulse oximetry, snoring and body position

Prevalence of SDB (% CHF pts)



Severity of SDB (% CHF pts)



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Sleep disordered breathing in HF

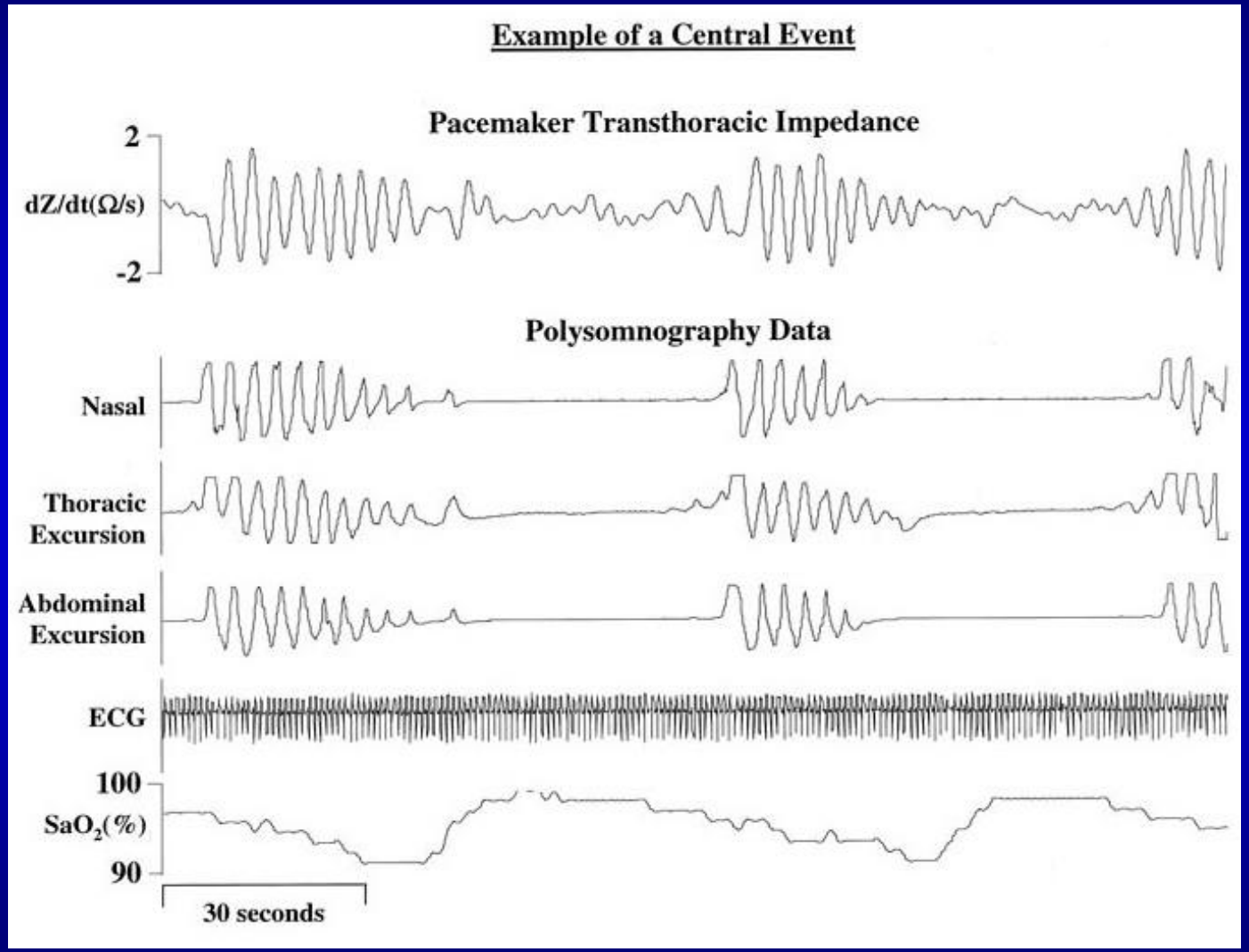
Diagnosis in cardiology practice

- **Polysomnography („gold standard”)**
  - sleep study / sleep laboratory
  - portable polysomnograph monitors
  - polygraphy / pulse oximetry
- **Questionnaires**
- **Other techniques**
  - heart rate (blood pressure) variability
  - thoracic bioimpedance (pacemakers)

Patients at High Risk for Central Sleep Apnea

- ✓ **Primary risk factors for Central Sleep Apnea**
  - ✓ Recent heart failure hospitalization
  - ✓ Chronic fatigue
  - ✓ Nocturia (> 2 per night)
  - ✓ Atrial fibrillation
  - ✓ Ventricular arrhythmias
  - ✓ Witnessed apneas
- ✓ **Additional risk factors (secondary)**
  - ✓ Male
  - ✓ Elderly
  - ✓ Lean
  - ✓ Decreased exercise tolerance
  - ✓ Low ejection fraction
    - » Paroxysmal nocturnal dyspnea (PND)
    - » Stroke
    - » Carotid stenosis
    - » Diabetes mellitus

Transthoracic Impedance Signals in Pacemakers



For the cutoff level of AHI >20/h, all patients were correctly classified by the pacemaker (100% specificity and sensitivity)

Scharf C, Circulation 2004

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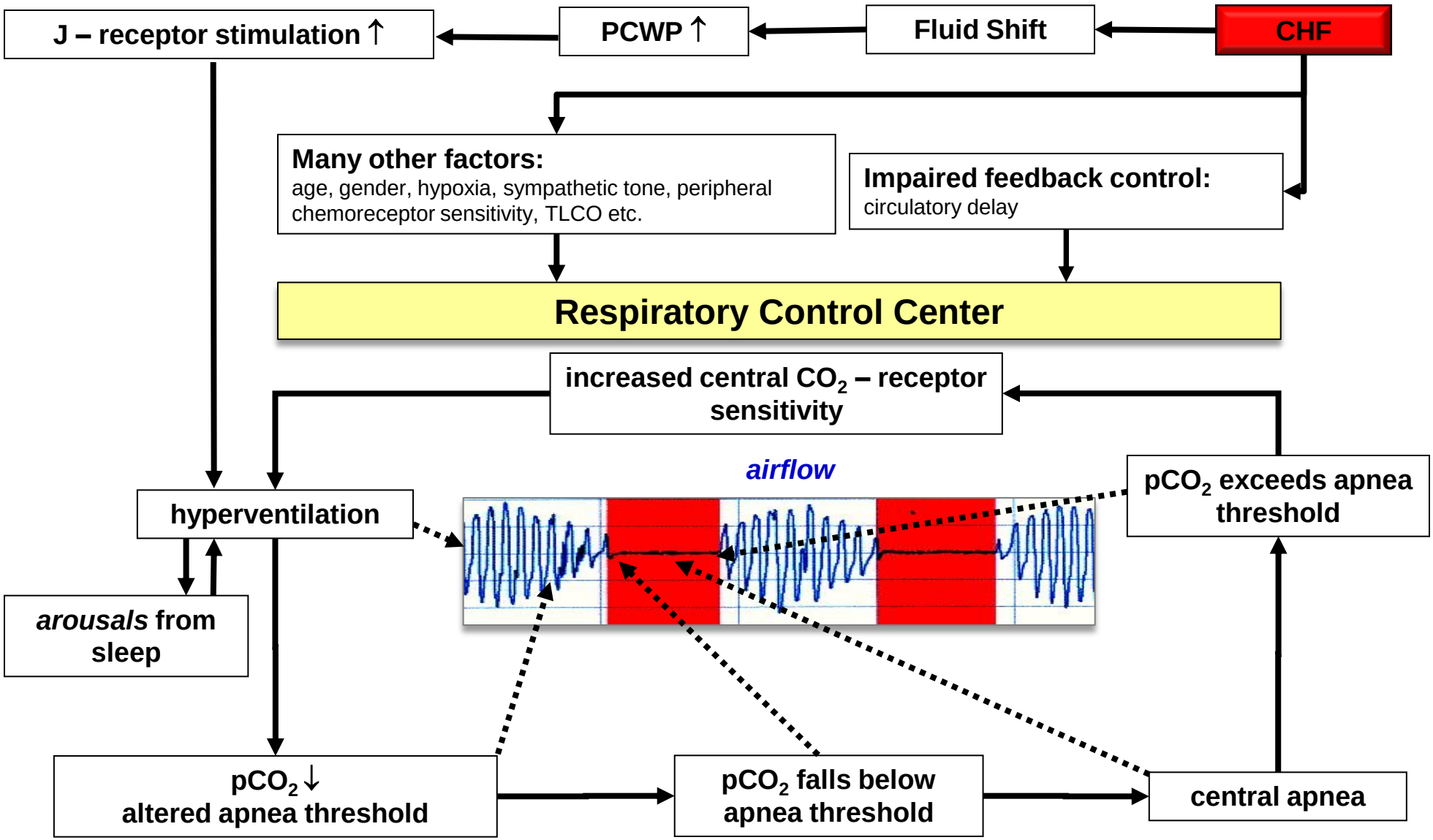
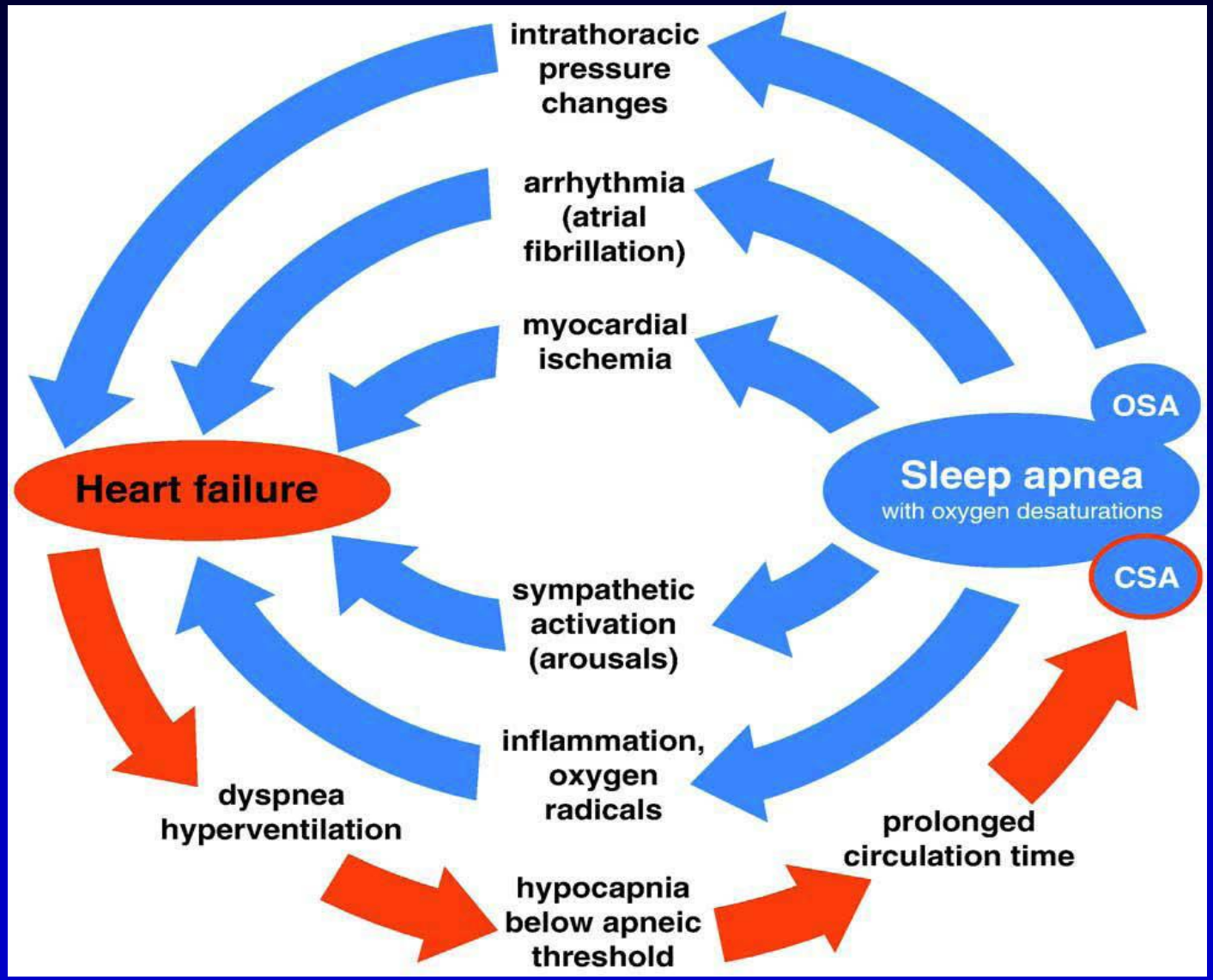
Pathophysiology of Cheyne-Stokes Respriation in CHF



O. Oldenburg, HFA meeting 2011

Cycle of SDB Intertwined with Cycle of Heart Failure



Brenner et al. *Trends Cardiovasc Med* 2008;18:240-7

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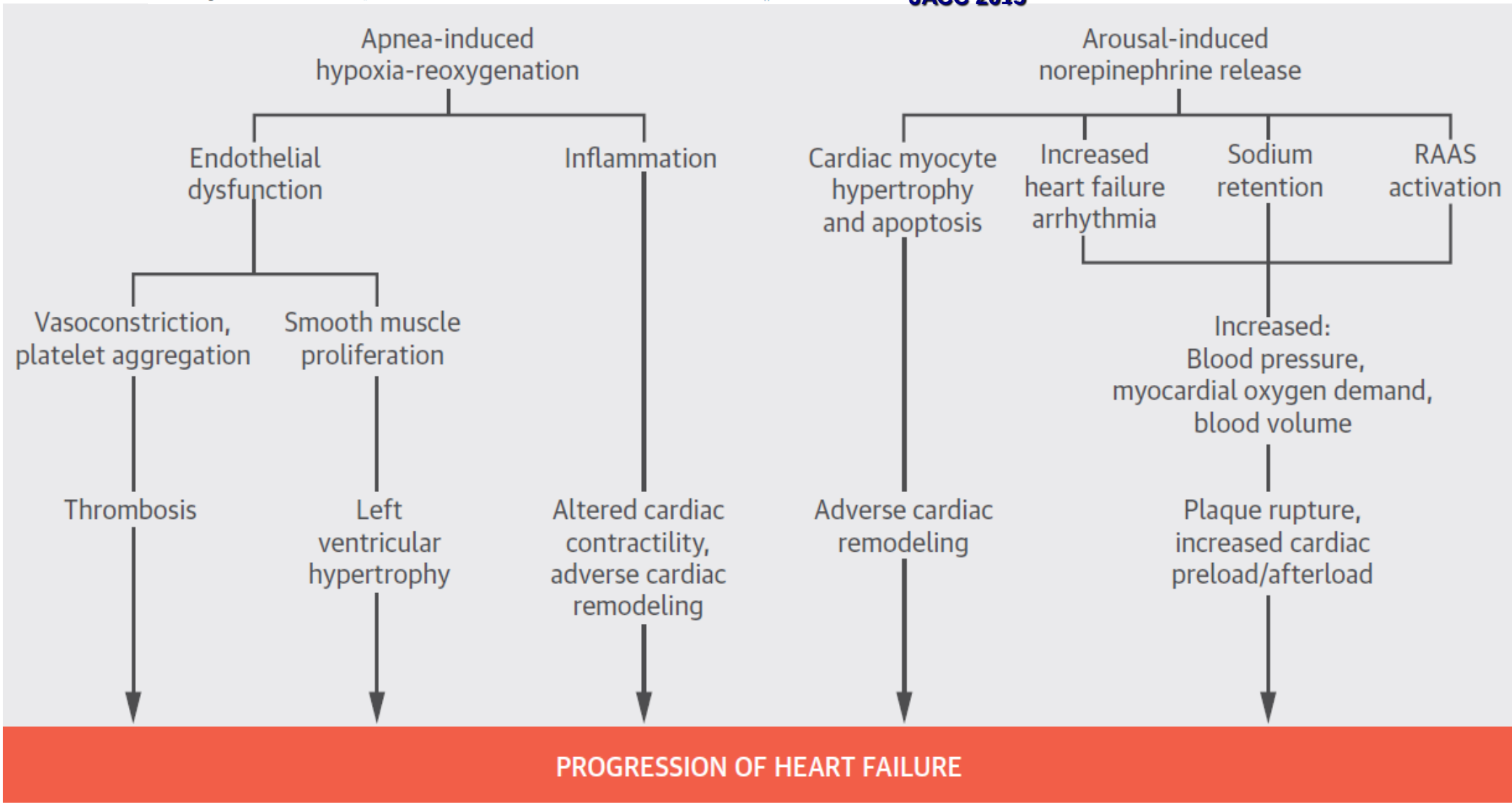
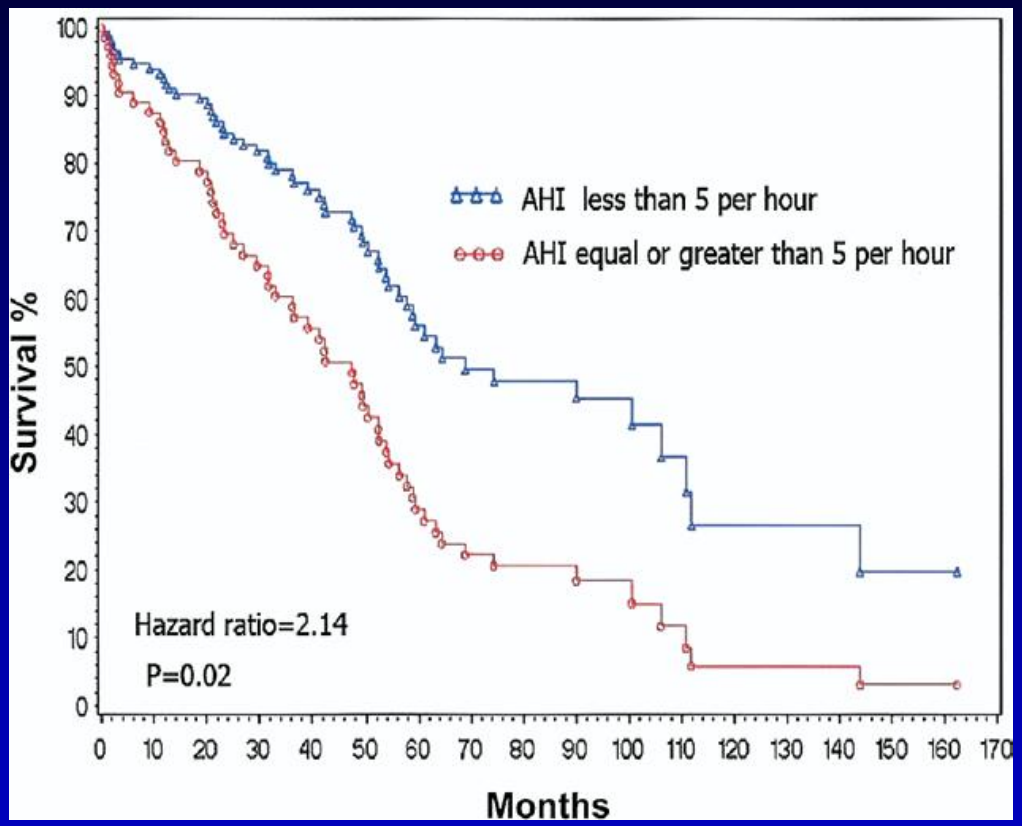
Mechanisms and Clinical Consequences of Untreated Central Sleep Apnea in Heart Failure

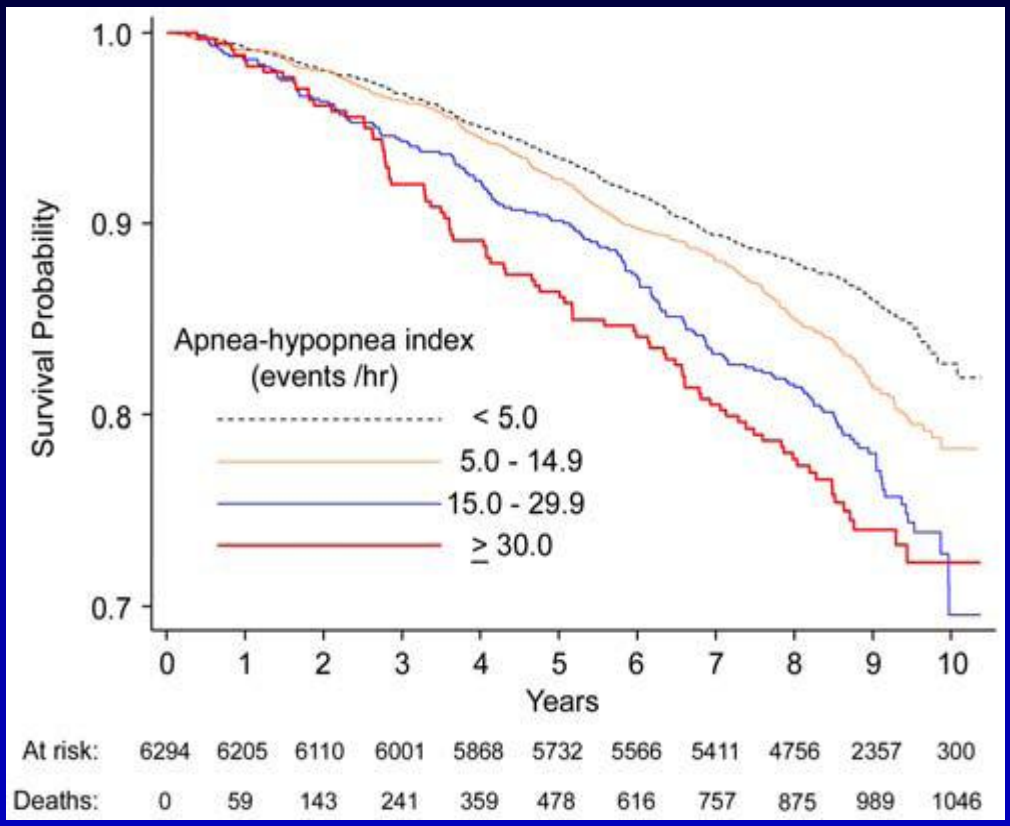
Maria Rosa Costanzo, MD,* Rami Khayat, MD,† Piotr Ponikowski, MD,‡§ Ralph Augostini, MD,‖
Christoph Stellbrink, MD,¶ Marcus Mianulli, BS,# William T. Abraham, MD‖

JACC 2015



CSA Increases Mortality in Heart Failure Patients





- Relationship of increased mortality and CSA constant across all levels of severity of CSA
- Mortality increases with increased AHI in patients with SDB
- Mortality remains high even with optimal current therapies

Javaheri et al. *JACC.* 2007;49:2028-34
Punjabi et al. *PLoS Medicine.* 2009;6:1-9

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Sleep Apnoea Management in Heart Failure

1. HF management optimization
2. Specific therapies:

   a. non-invasive ventilatory support (CPAP, ASV)

   b. nocturnal O_2 / CO_2 supplementation

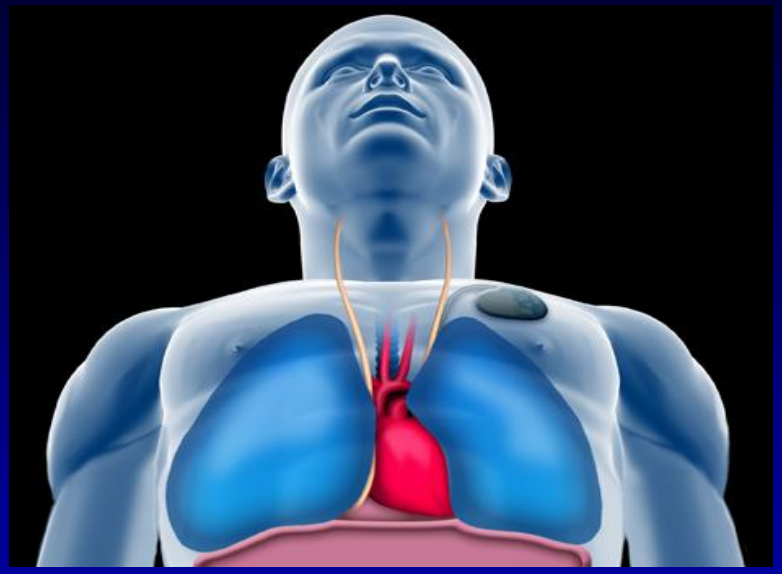
   c. drugs: theophylline, acetazolamide

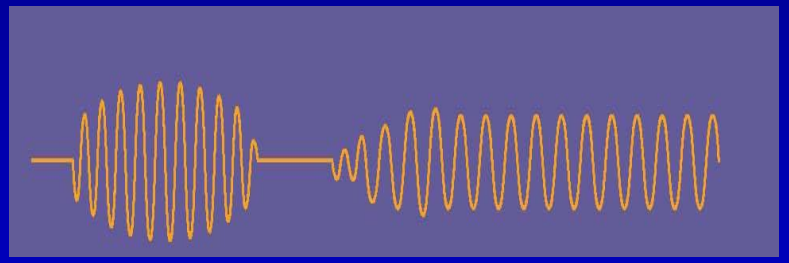
   d. devices: cardiac pacing (CRT, atrial overdrive pacing), phrenic nerve stimulation,

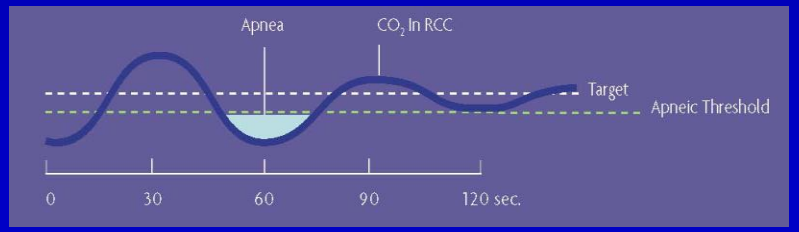
Positive Airway Pressure Therapies

- **CPAP (Continuous Positive Airway Pressure)**
  - CSA episodes not reduced 100% (30-50%)
  - Requires patient compliance
  - Does not affect M&M
  - May worsen heart failure
- **ASV (Adaptive Servo Ventilation)**
  - CPAP with changes in O_2 pressure to meet patient need
  - Pressure on right side of heart may increase
  - Compliance & tolerance ms
  - In clinical trials

A New Therapeutic Concept





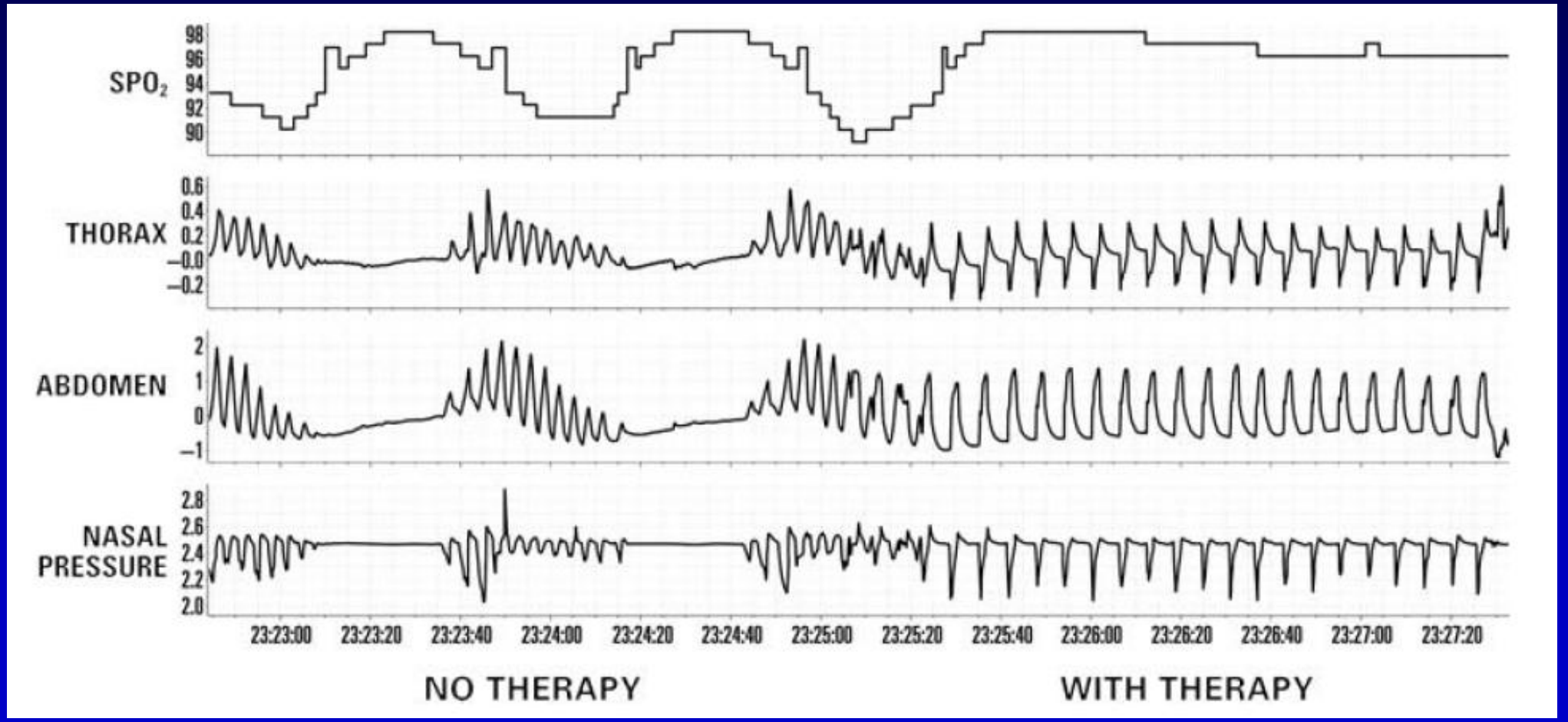


Goal: Restore normal breathing at night

- Phrenic nerve stimulation can be used to modulate diaphragmatic contraction and affect breathing.

- We hypothesized that stimulation of the phrenic nerve during a central event could be used to initiate inspiration or increase inspiratory time, halting or preventing the apnoea.

Elimination of respiratory instability and improvement in oxygenation during unilateral phrenic nerve stimulation in a HF patients with central sleep apnea



Ponikowski P et al. Eur Heart J 2012;33:889-94

The remedē® System Regularizes Breathing During Sleep

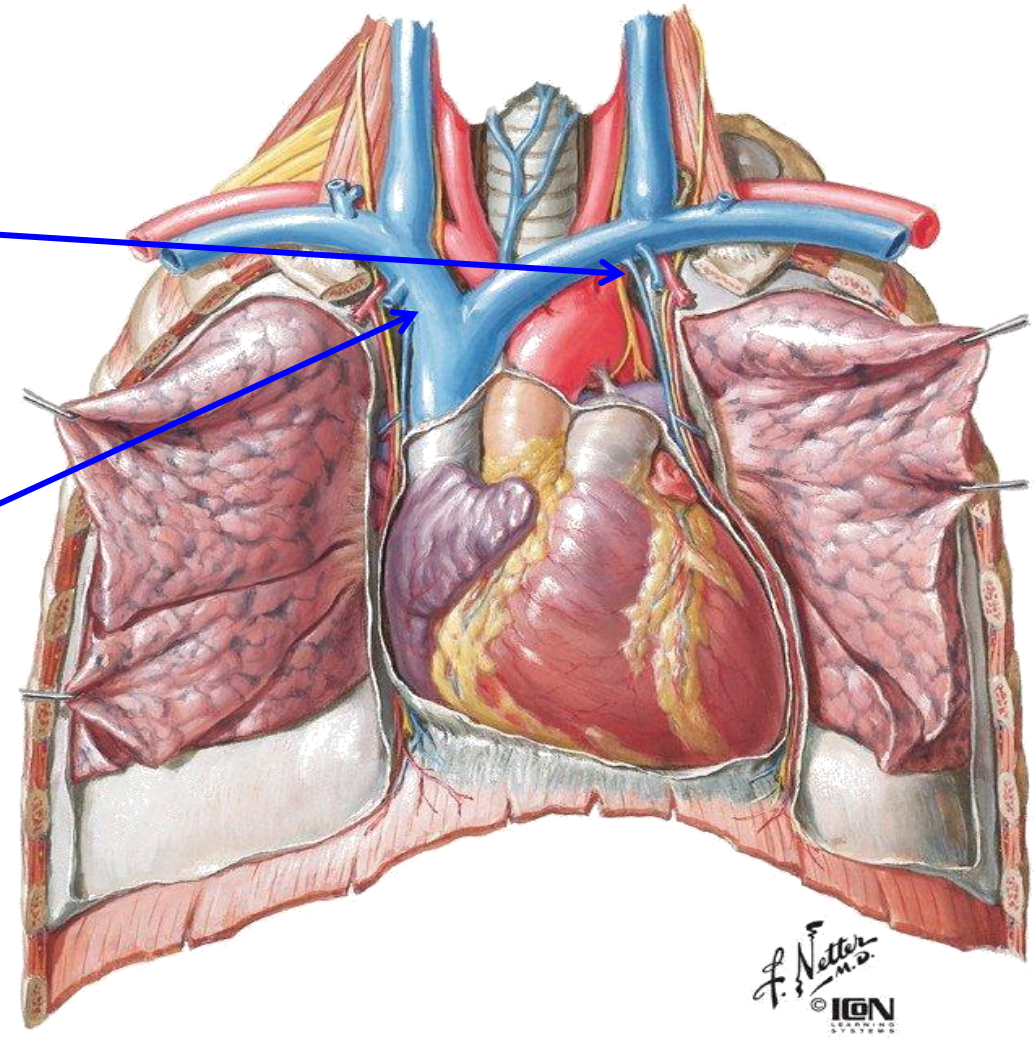
The remedē® System:

- Novel neurostimulation device *transvenously implanted* like a cardiac device
- Contracts the diaphragm via *unilateral stimulation* of the phrenic nerve
- Stabilizes carbon dioxide and *restores a normal breathing pattern*
- *Activates automatically* during sleep

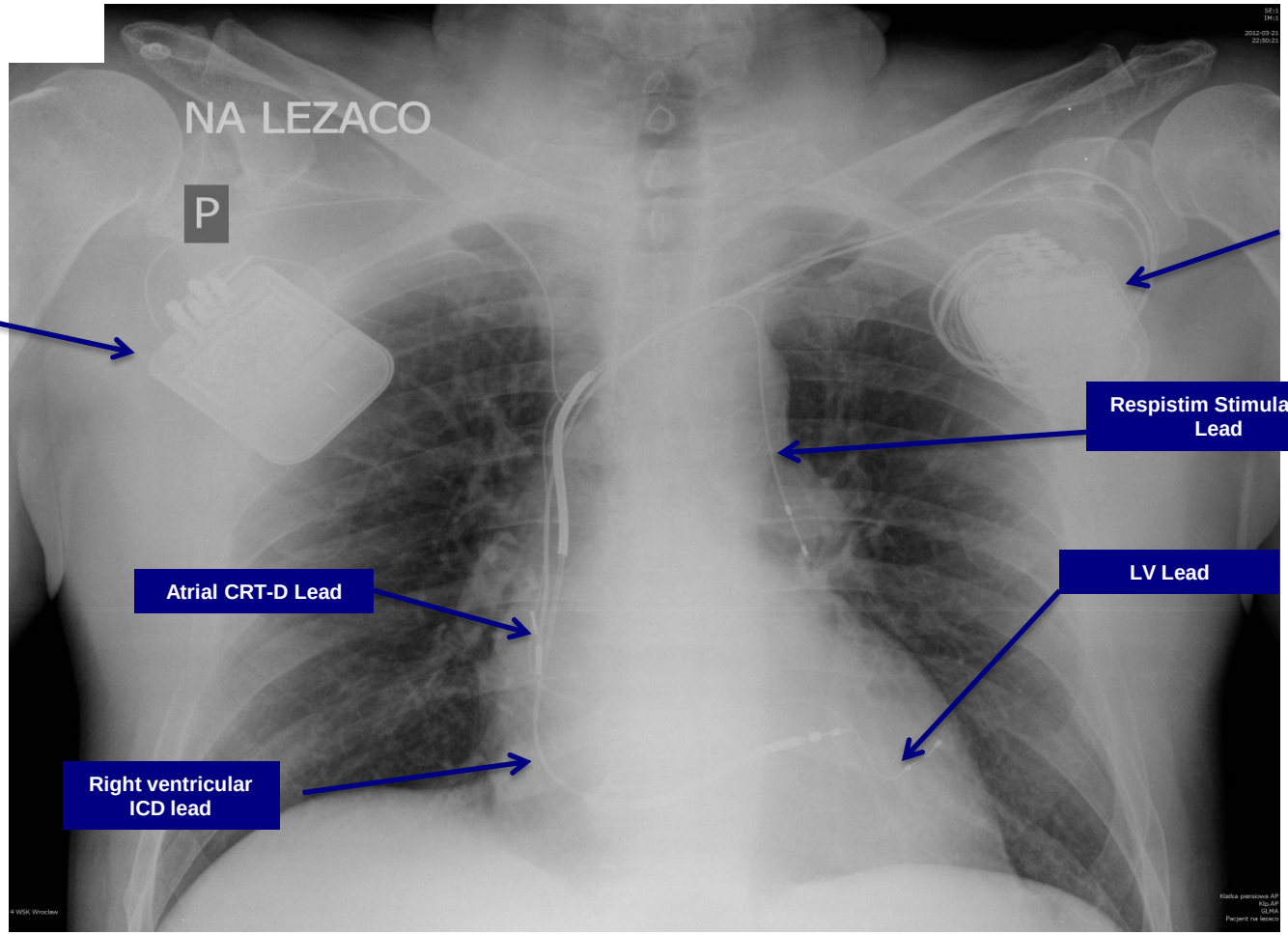
remedē® System Can Provide Unilateral Stimulation From Two Locations

2 stimulation locations

- Left Pericardiophrenic Vein
- Right Brachiocephalic Vein



Chest X-ray of the remedē® System with CRT-D



remedē® System Pulse Generator

CRT-D Pulse Generator

Respistim Stimulation Lead

LV Lead

Atrial CRT-D Lead

Right ventricular ICD lead

[USA] CAUTION: Investigational Device. Federal (or United States) law limits this device to investigational use.

The **rem**edē® System Pilot Study: Key Effects on Sleep Parameters at 3 and 6 Months

Parameter	Baseline*	3 Months*	6 Months*	P Value
Apnea-hypopnea index (AHI), no./hr of sleep	**49±15**	**23±14**	**23±13**	**≤ 0.0001†**
Central apnea index (CAI), no./hr of sleep	**28±15**	**5±9**	**5±7**	**<0.0001†**
Obstructive apnea index (OAI), no./hr of sleep	3±3	4±5	4±5	0.0223‡
Mixed apnea index (MAI), no./hr of sleep	3±4	0±1	1±2	<0.0002†
Hypopnea index (HI), no./hr of sleep	15±12	14±9	14±8	0.0179‡
4% Oxygen desaturation index (ODI4), no./hr of sleep	46±19	22±14	23±13	<0.0001†
Arousal index, no./hr of sleep	36±18	23±11	25±12	<0.0001†
Sleep efficiency, %	69±17	77±16	81±13	<0.0001†
Rapid eye movement (REM) sleep, %	11±6	16±8	17±7	<0.0001†

N = 44 subjects
*All values expressed as mean±SD.
† Repeated measures ANOVA.
‡ Friedman test.

Abraham et al. HFSA 2013

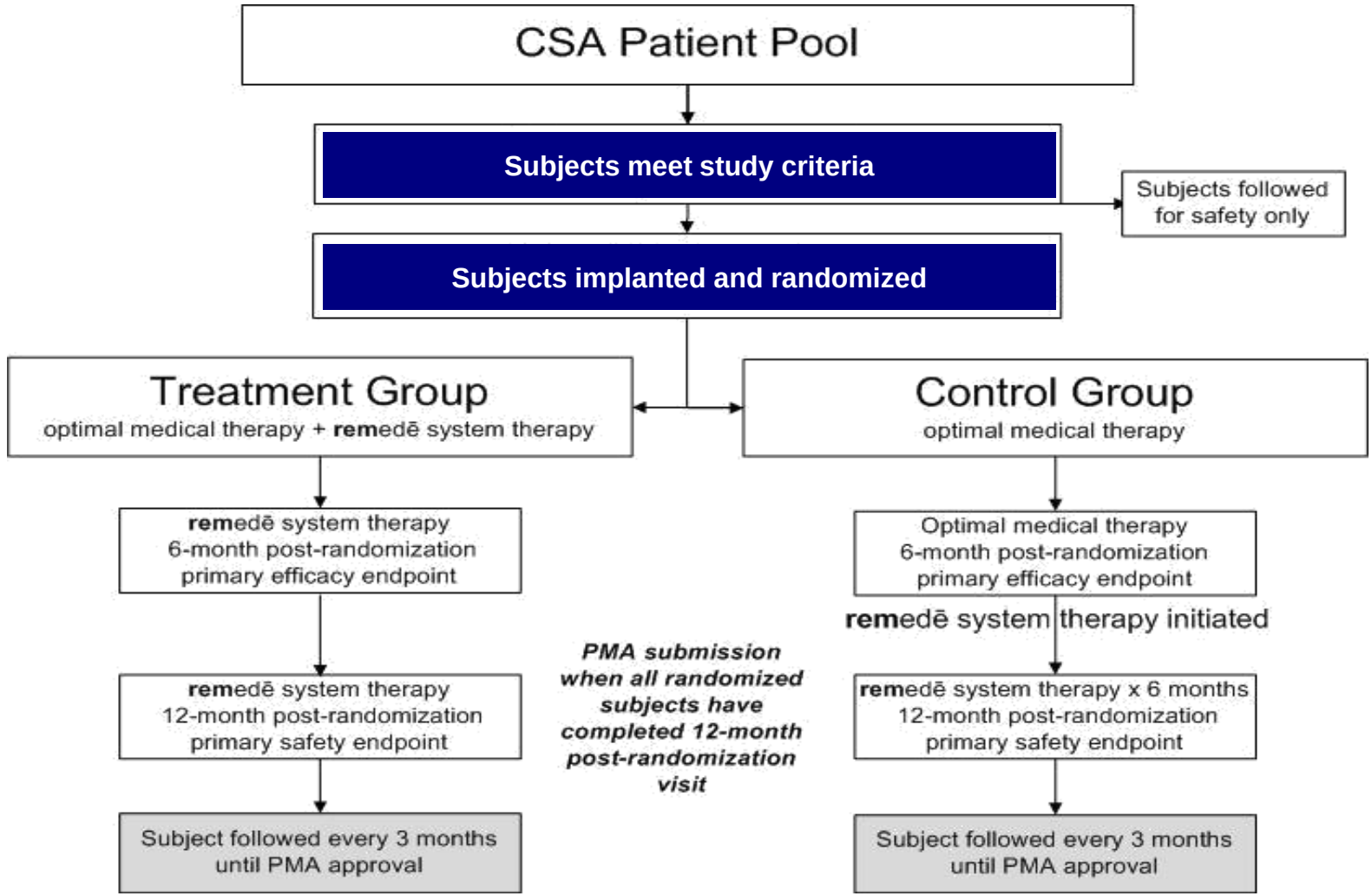
Randomized Controlled Pivotal Trial: Purpose and Endpoints

- Purpose: Evaluate the safety and effectiveness of the therapy delivered by the remedē System in subjects with moderate to severe central sleep apnea (CSA)

1:1 randomization, 147 subjects followed to 12 months, 25 US sites, additional OUS sites

- Primary Endpoints:
  - » Effectiveness: Proportion of subjects that achieve a ≥50% reduction in AHI from baseline to 6 months post randomization (Treatment vs Control)
  - » Safety: Freedom from serious adverse events (SAEs) associated with the implant procedure, the remedē System, or the delivered therapy at 12 months

Pivotal Trial Design



Sleep apnoea in heart failure - summary

1. Present as OSA or CSA (specific for HF syndrome)
2. Prevalent (affects more than 50% HF pts),
   but still under-recognized among cardiologists
3. Diagnosis possible in the everyday cardiology practice
4. Ominous pathophysiological and clinical consequences
   (progression of the disease, increased M&M)
5. Potential therapeutic target in HF