A Deadly Combination: Central Sleep Apnea & Heart Failure

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Disclosures

- Boston Scientific: fellowship support, speaking honoraria
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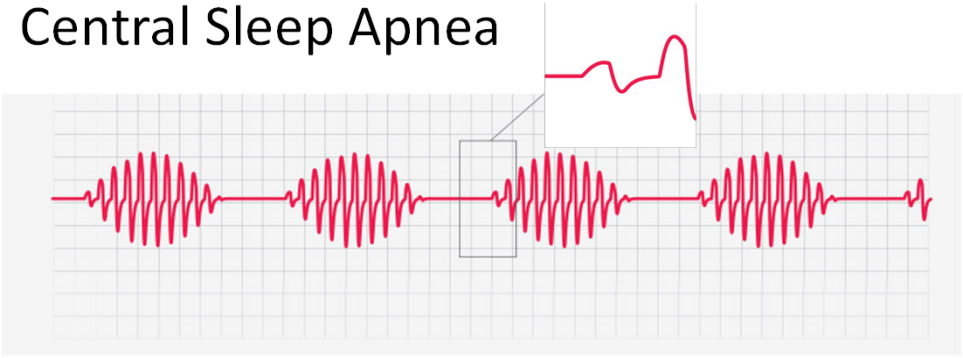
- Abbott/St. Jude Medical: research grant
- Bristol-Meyers-Squibb: research grant

Overview

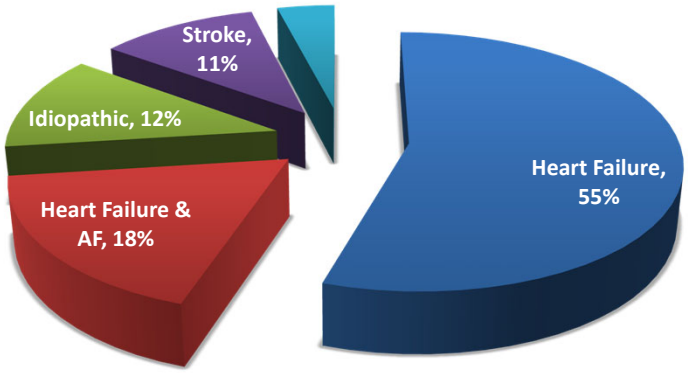
- Defining Central Sleep Apnea (CSA)
- Diagnosing Central Sleep Apnea
- Deadly Combination of Central Sleep Apnea and Heart Failure
- Device based therapy: remede® system
  - Pivotal Trial Results
- Discussion

Central Sleep Apnea

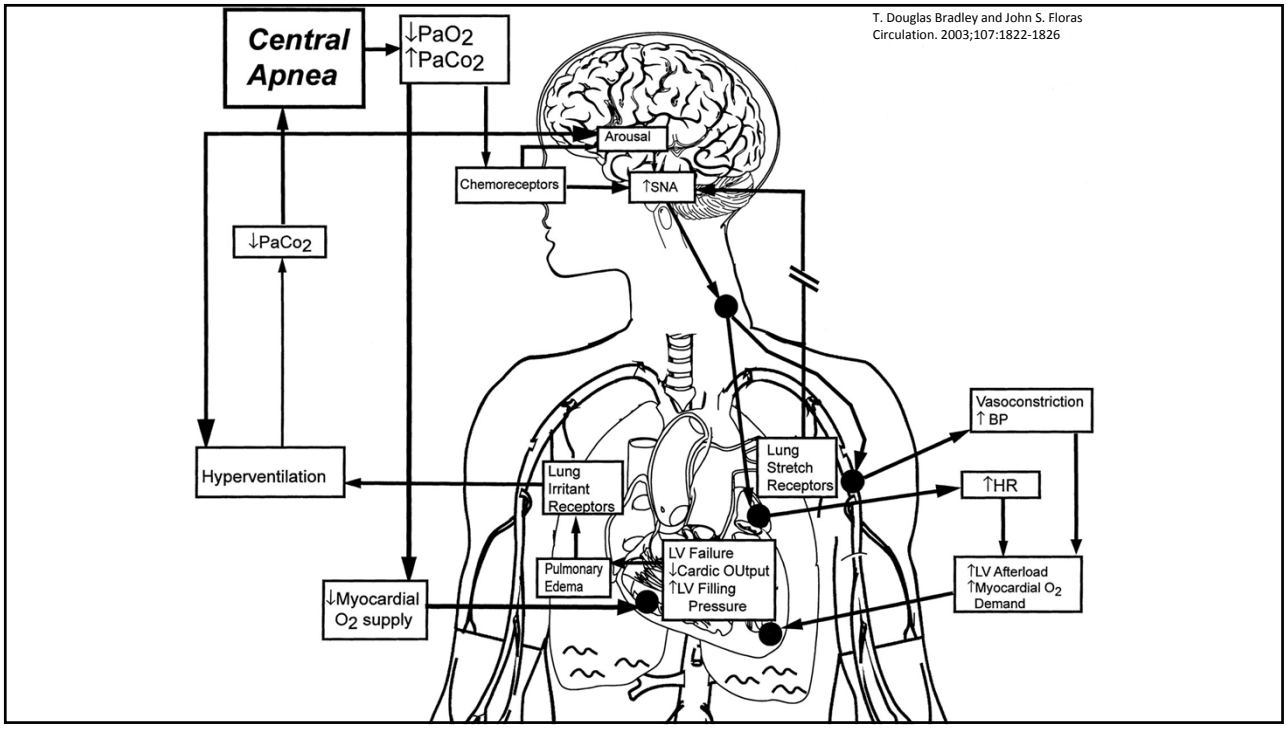


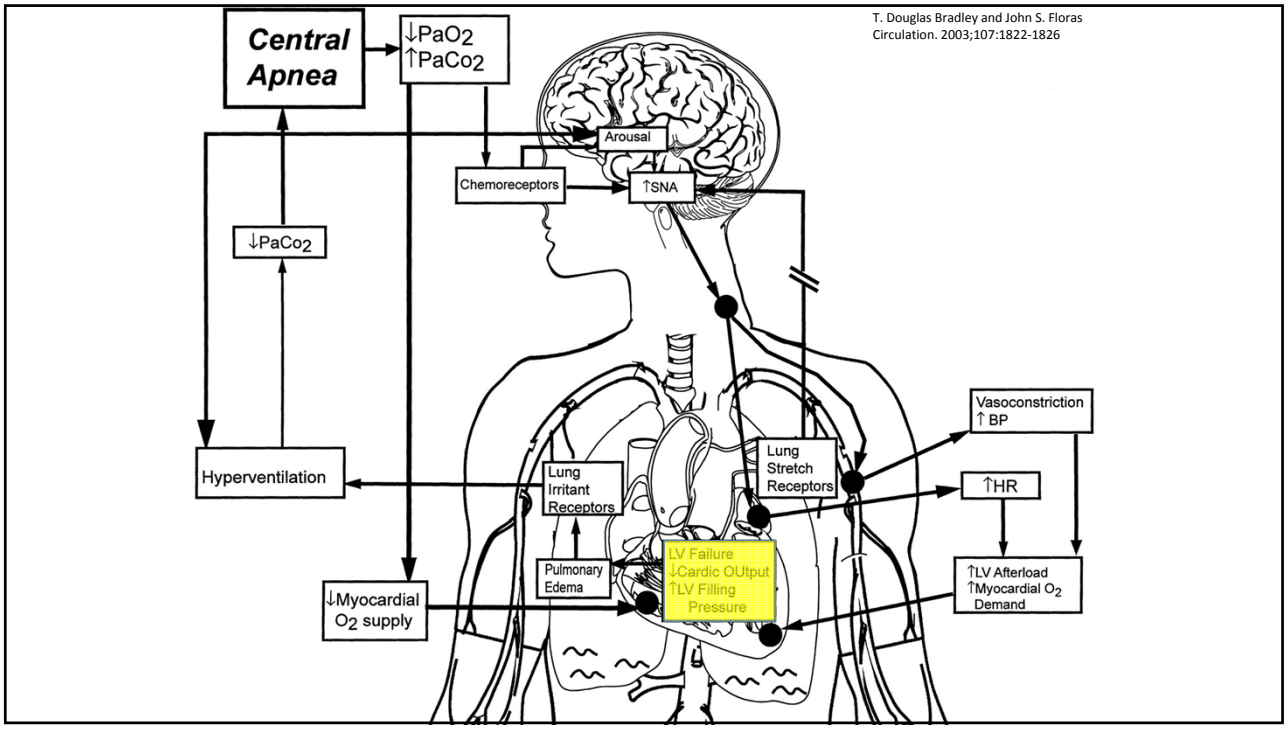
- A central apnea is a >10 second pause in ventilation with **NO** associated respiratory effort
- It results from an intermittent neural drive to breathe resulting in a periodic breathing pattern
- Patients with heart failure, atrial fibrillation and stroke are at increased risk for development of central sleep apnea (CSA)

Central Sleep Apnea Comorbidities



- Many patients with central sleep apnea have concomitant cardiovascular disease

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Circulation. 2003;107:1822-1826
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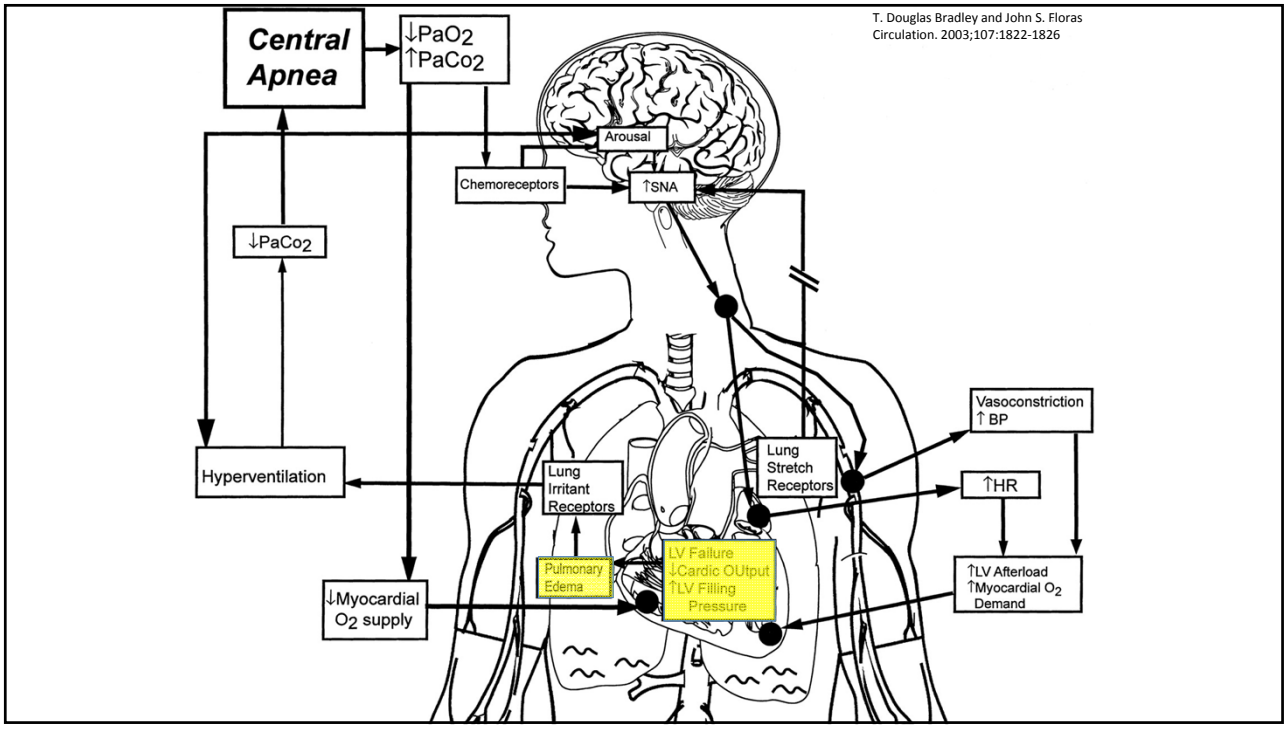
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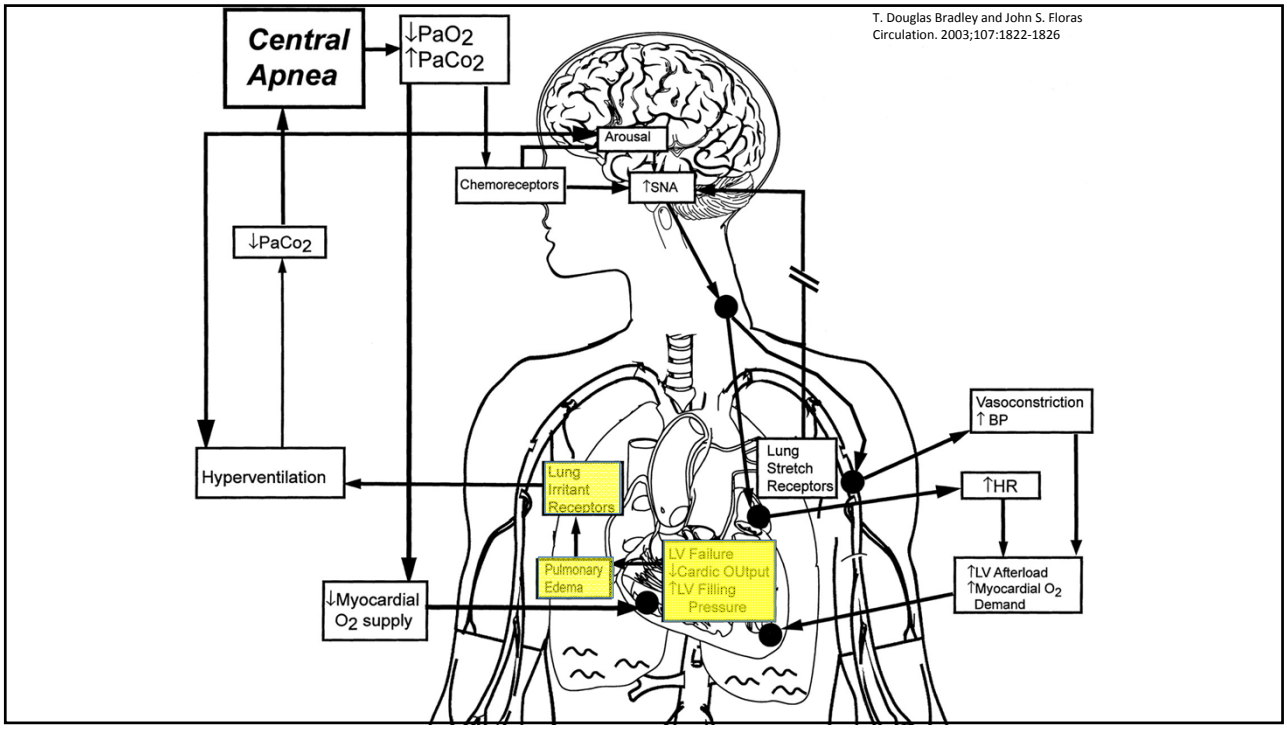
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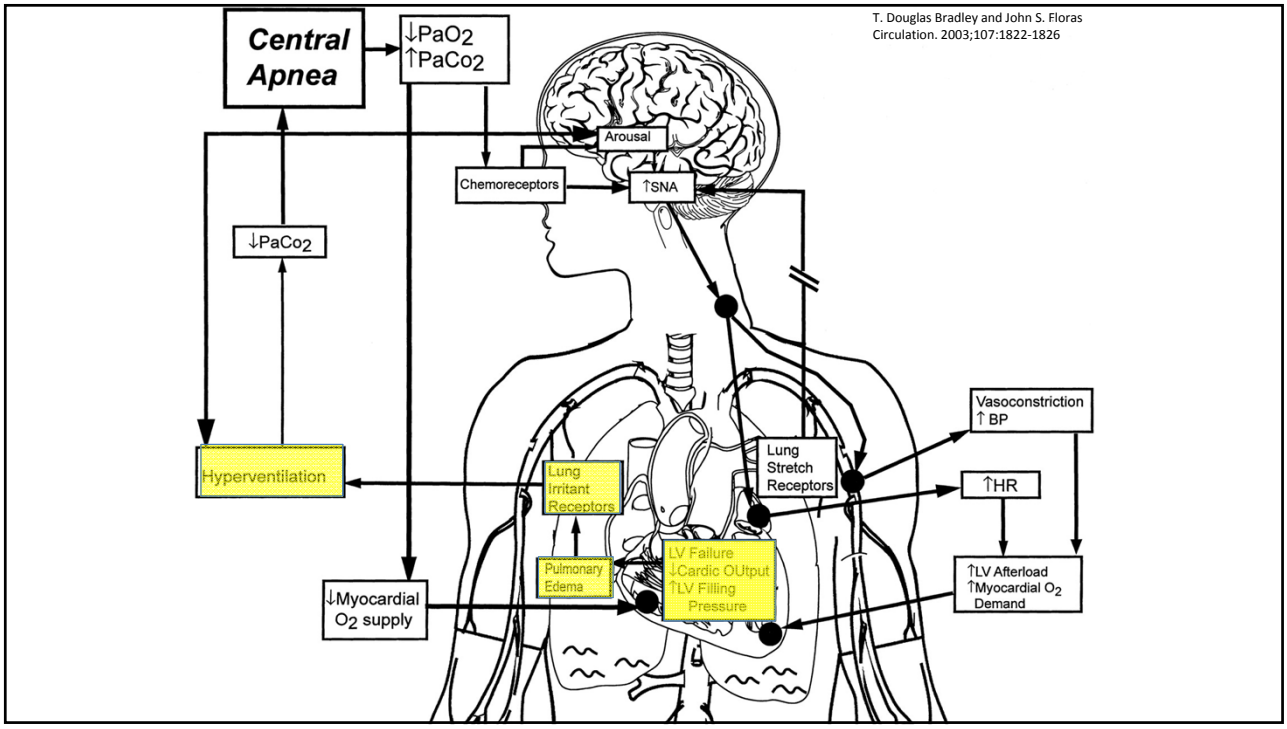
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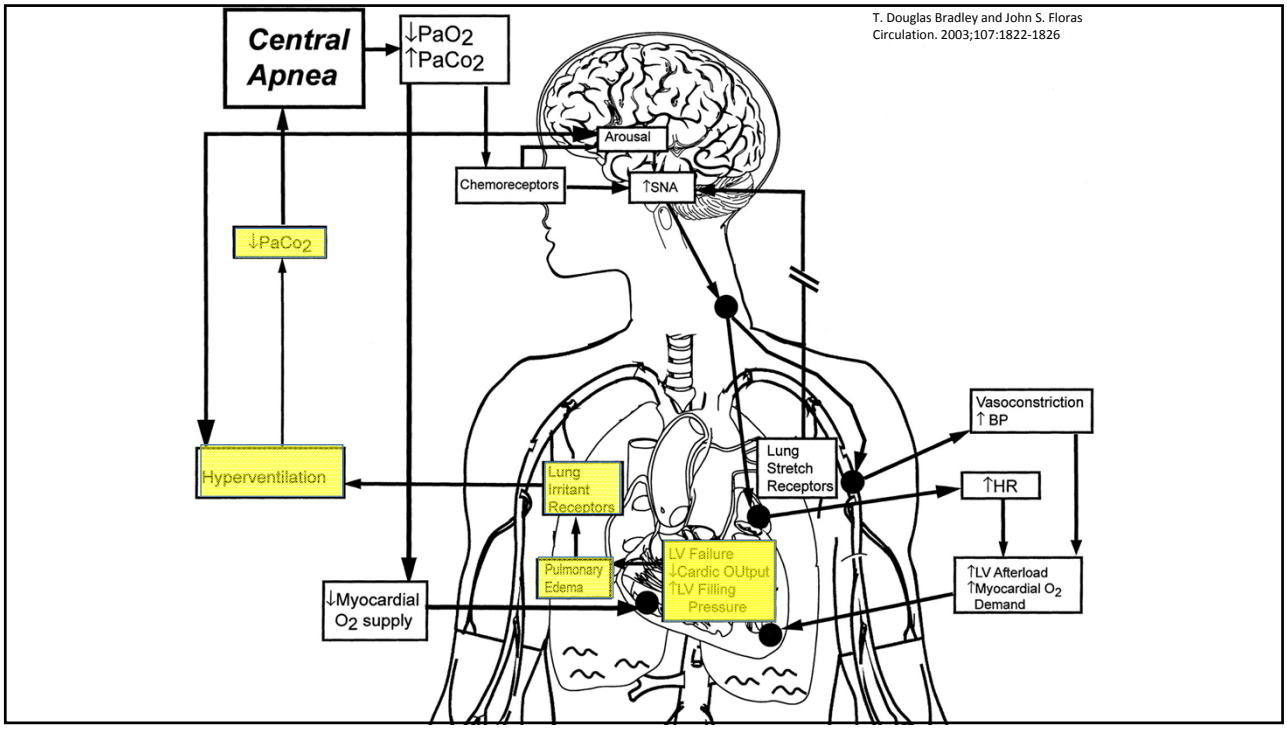
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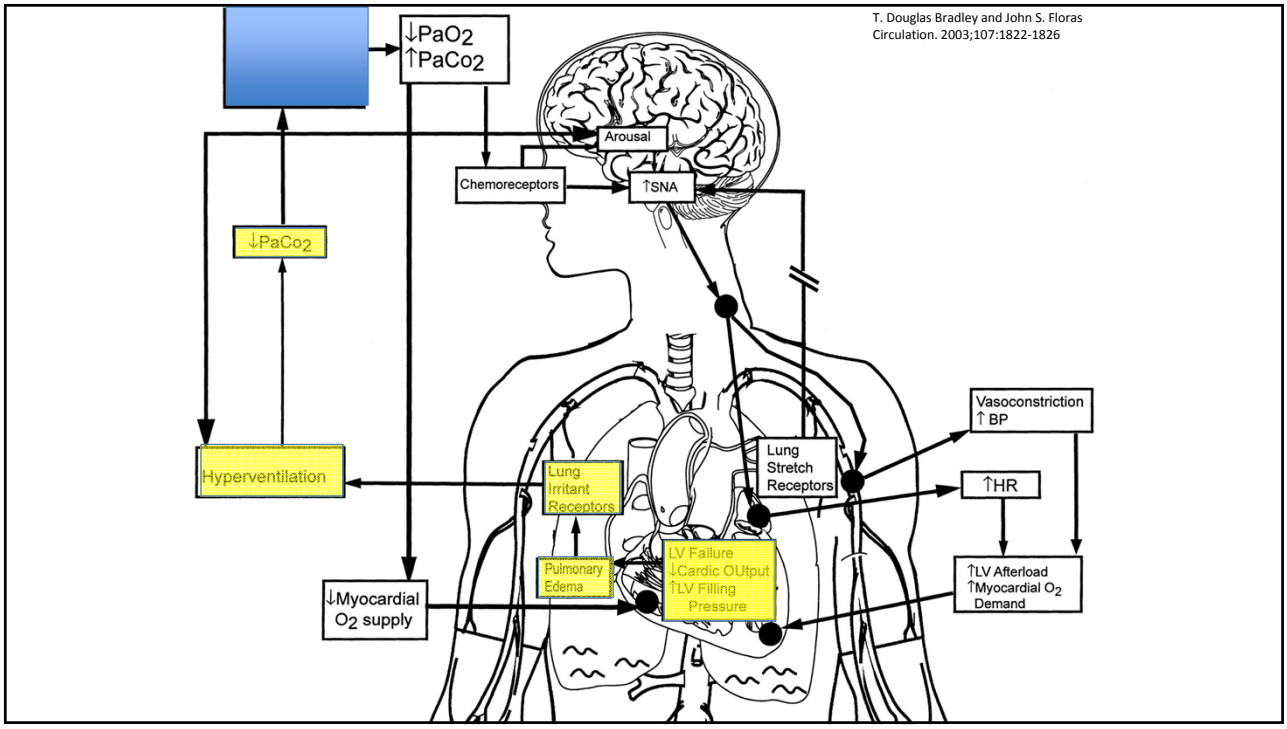
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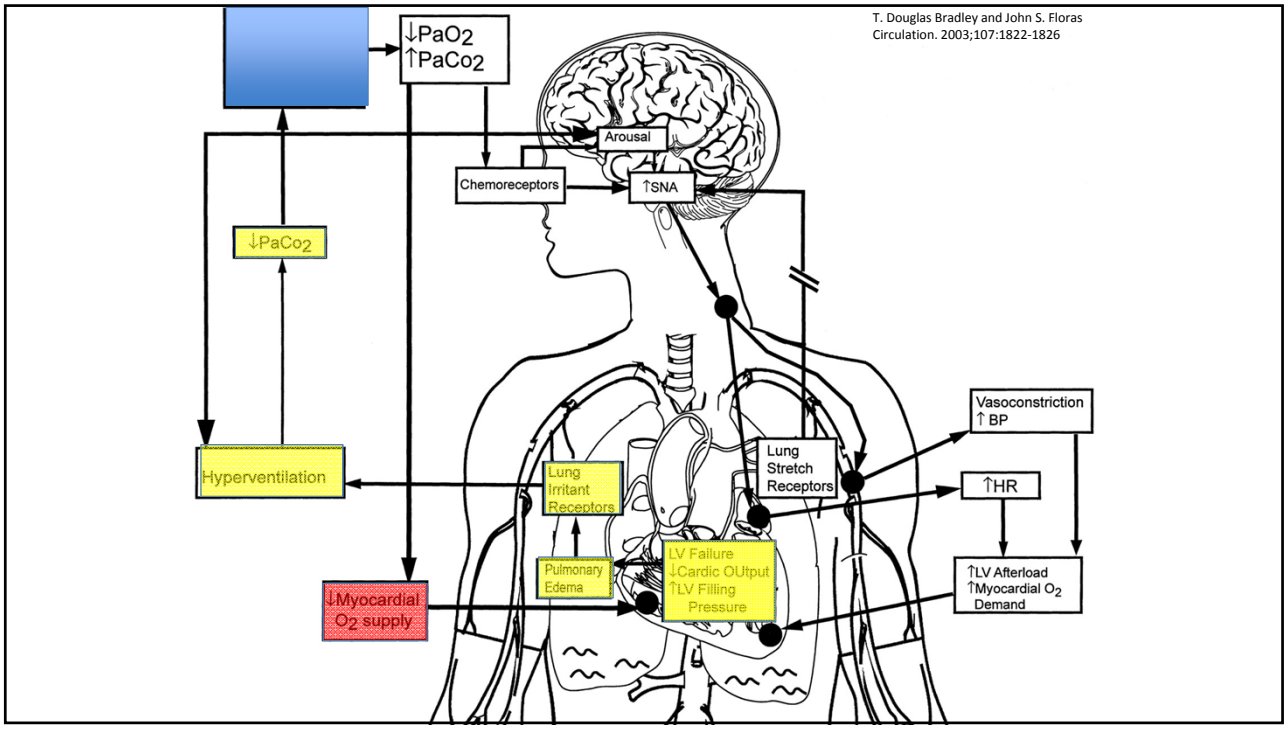
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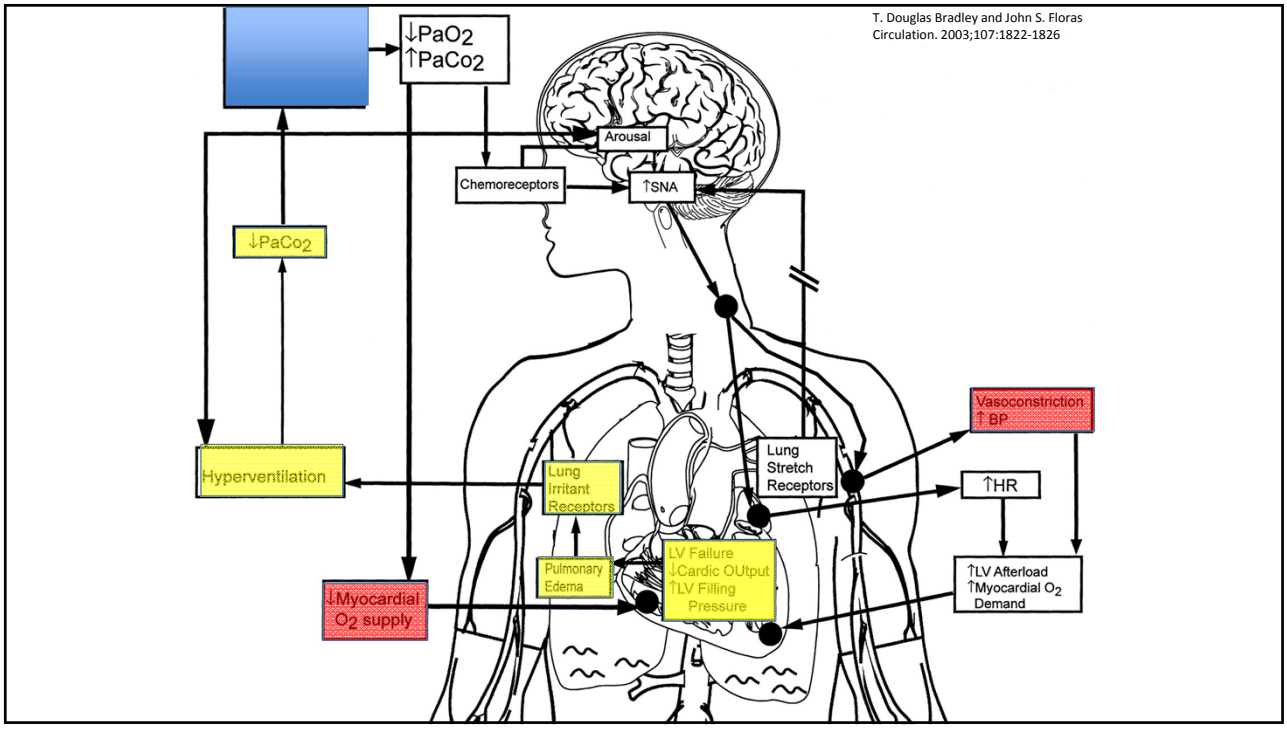
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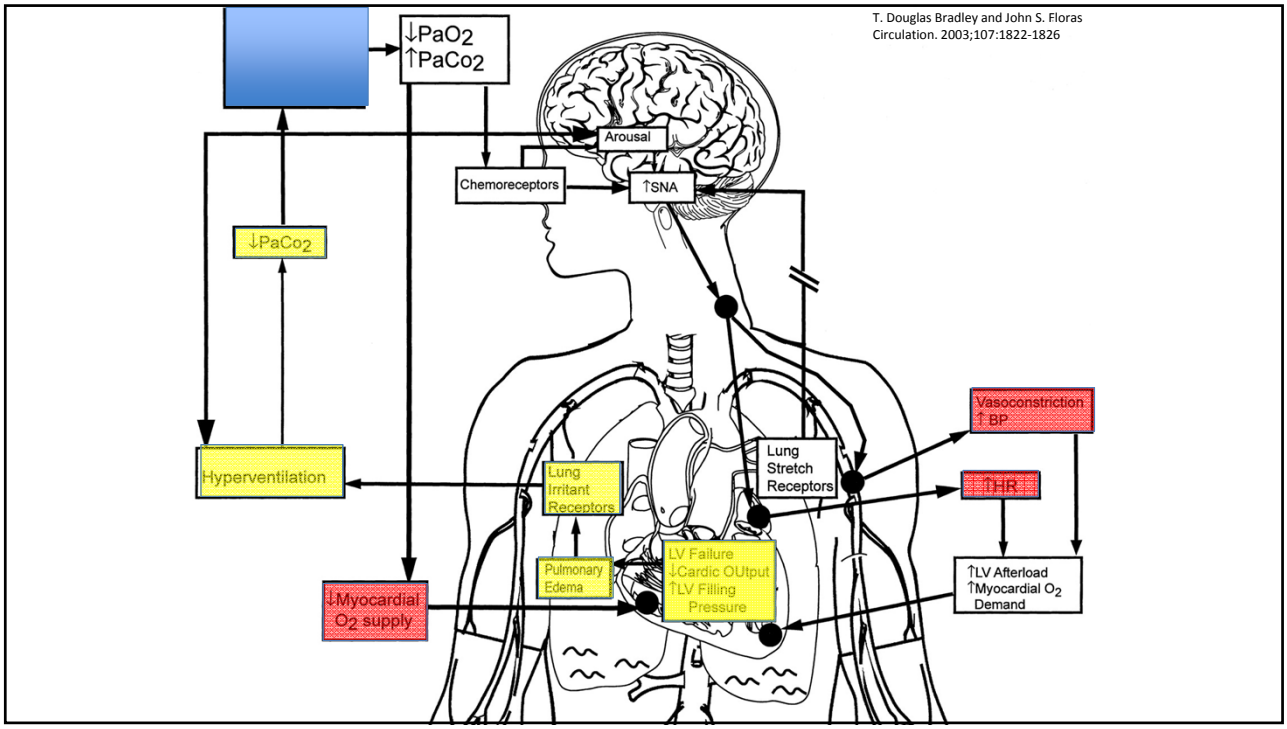
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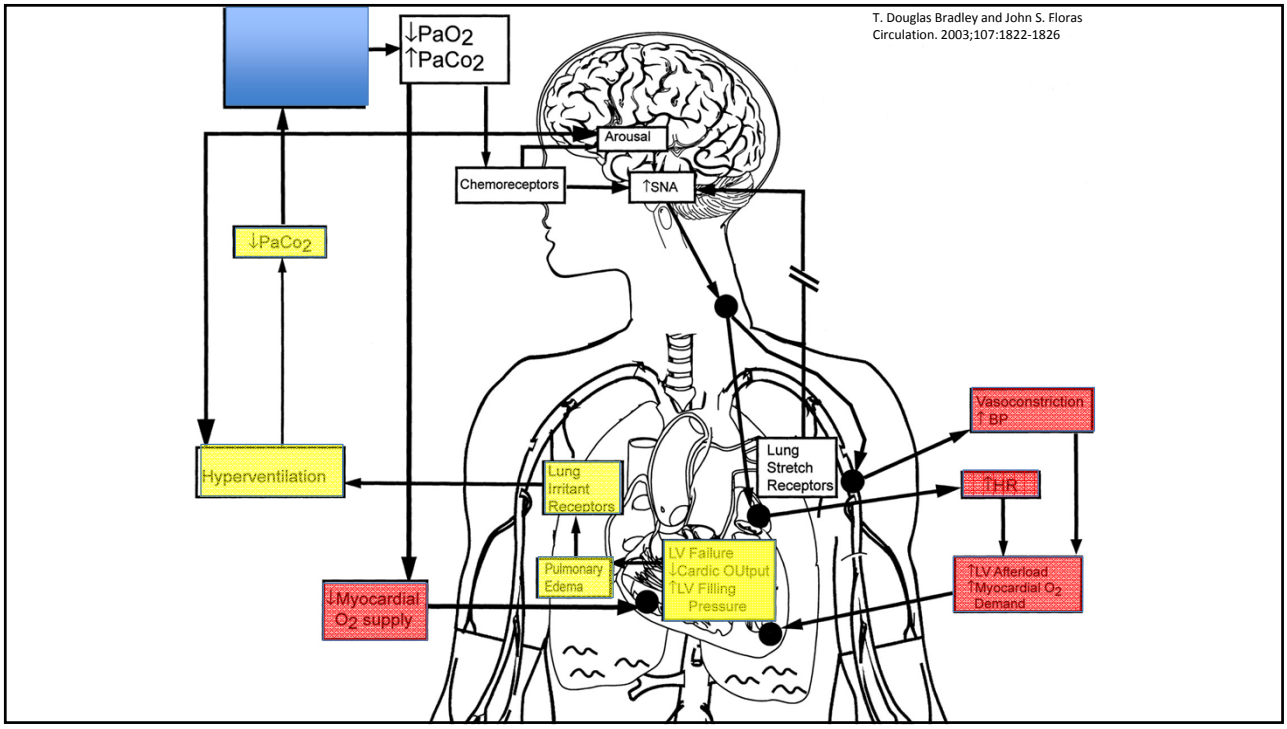
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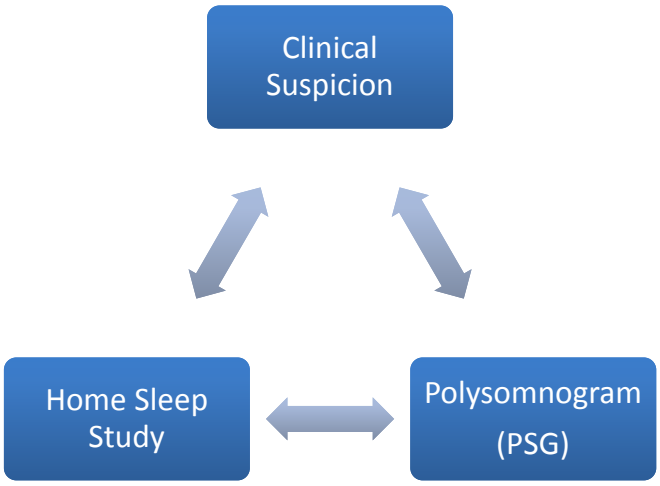
Screening for Central Sleep Apnea

	Adjusted Odds Ratio (95% Confidence Interval)
Male	4.33 (2.5-7.52)
Awake PCO2 < 38mmHg	4.33 (2.5-7.52)
Atrial Fibrillation	4.08 (1.74-9.57)
Age > 60 years	2.37 (1.35-4.15)

Screening for Central Sleep Apnea

Diagnosis of Central Sleep Apnea



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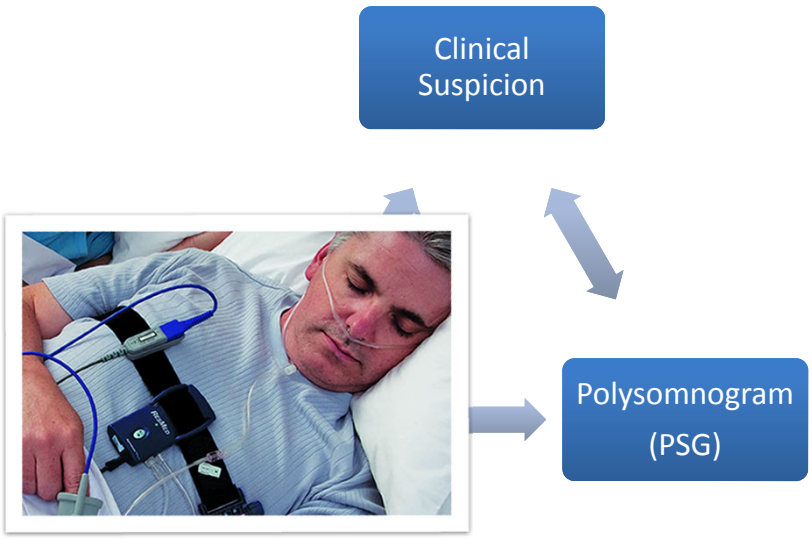

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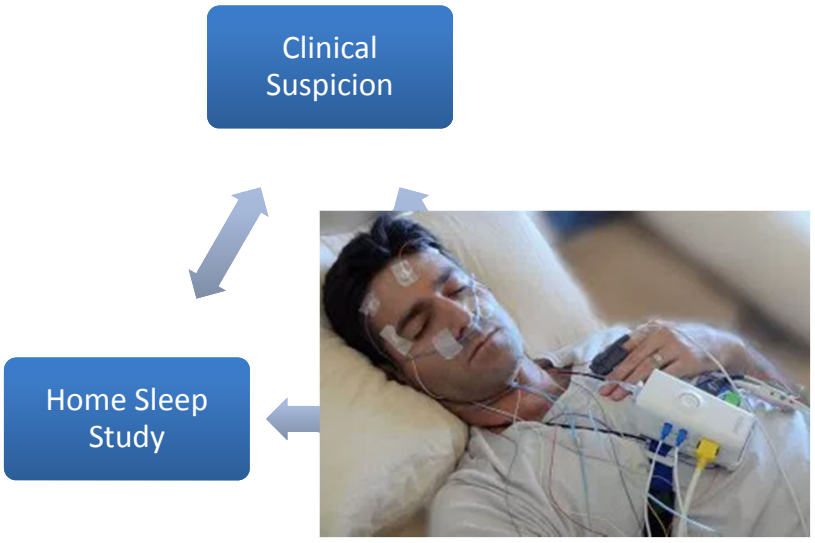


Sleep Study Interpretation

Number of Apnea/Hypopneas per Hour

- Apnea-Hypopnea Index (AHI): Overall number of apneas and hypopneas per hour of sleep
  - Apnea is defined as >10 second pause in respiration
  - Hypopnea is a decrease but not complete cessation of ventilation to less than 50% of normal, with associated fall in oxygen saturation or arousal
- Oxygen Desaturation Index (ODI4):
  - Apnea/hypopneas with an associated oxyhemoglobin desaturation greater than 4% are associated with cardiovascular disease independent of confounding variables

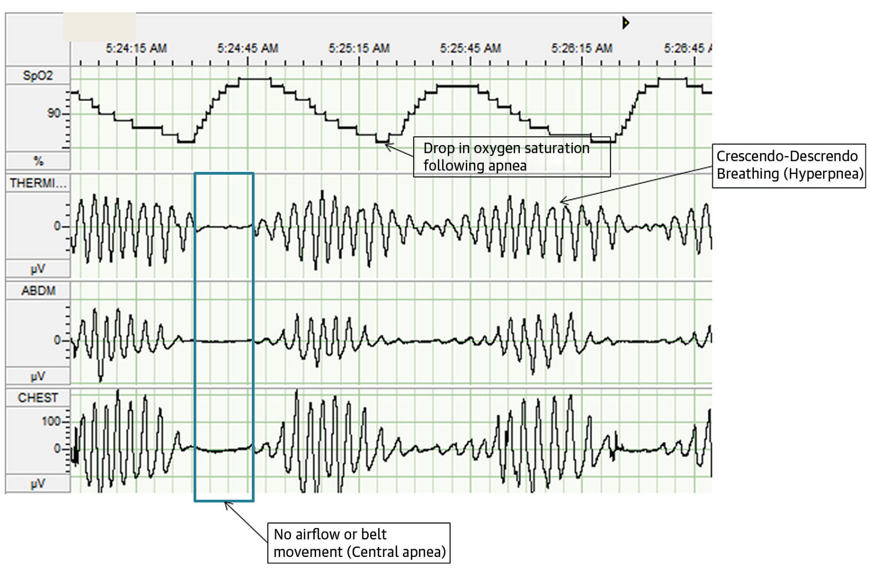
Sleep Study Interpretation

Central Apnea Index (CAI):

- Number of central apneas per hour
- Central sleep apnea is diagnosed when the number of central events > obstructive events

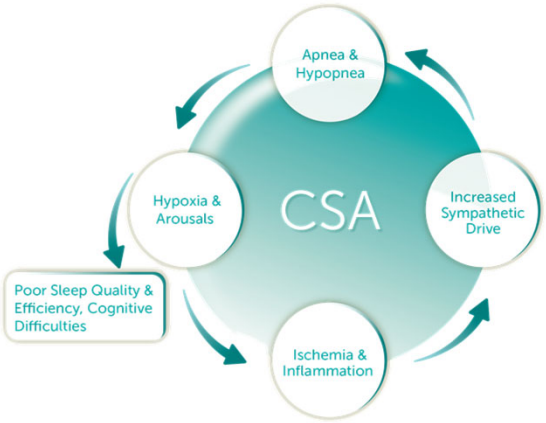
greater than 4% are associated with cardiovascular disease independent of confounding variables

Polysomnogram of Heart Failure Patient with Central Sleep Apnea



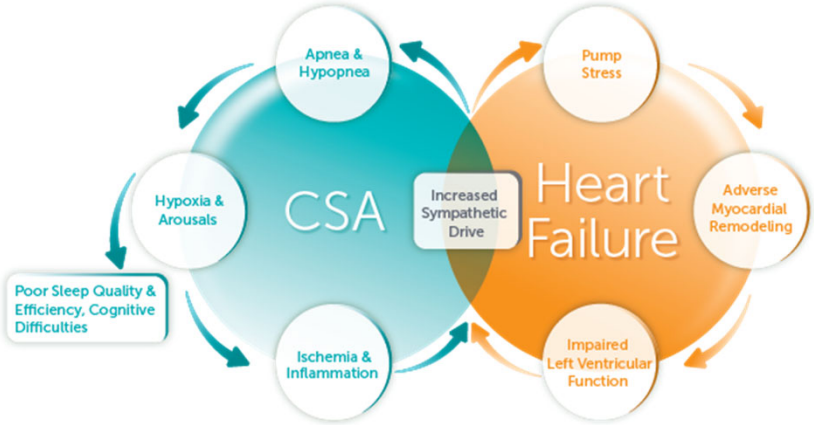
Journal of the American College of Cardiology, ISSN: 1558-3597, Vol: 65, Issue: 1, Page: 72-84 Publication Year: 2015 - (CC BY-NC-ND 4.0)

The Central Sleep Apnea Cycle



Somers NEJM 1993; Eltzscig, NEJM, 2011; Yaffe, JAMA, 2011; Lavie, Eur Resp J, 2009; Bitter, Eur H J, 2011; Costanzo et al., JACC, 2015

Effects of Central Sleep Apnea & Heart Failure are Intertwined



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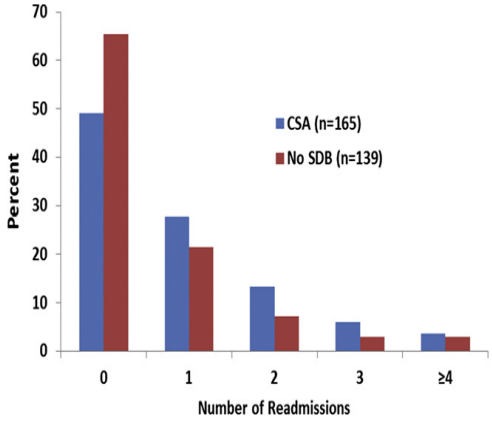
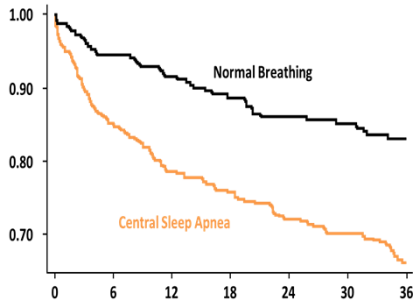
Readmissions and Mortality in Heart Failure Patients with CSA

- *Over 25% of hospitalized heart failure patients with central sleep apnea had 2 or more readmissions within 6 months*



- *Central sleep apnea is an independent predictor of mortality*



J Card Fail. 2012 Jul;18(7):534-40

Two strategies to treat central sleep apnoea in heart failure.

Treatments:

- Continuous positive airway pressure (CPAP)
- Adaptive servo-ventilation

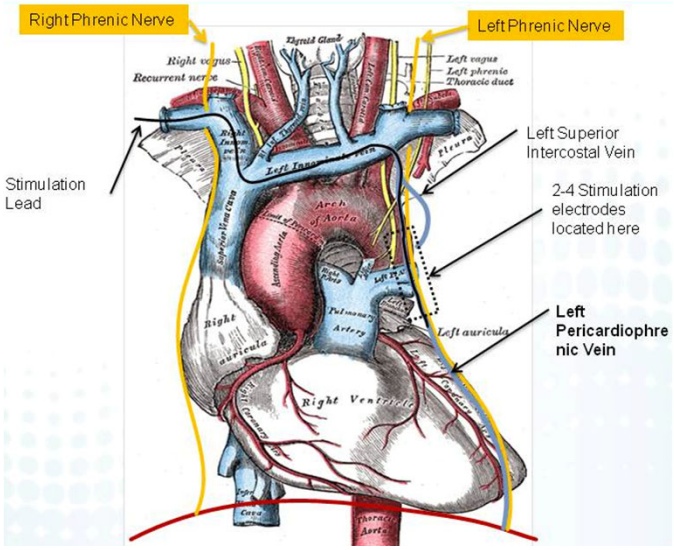
See the following Journal article for more information:
John S. Floras Eur Heart J 2012;33:810-812

Sleep Apnea & Heart Failure: Guidelines

III: Harm / B-R See Online Data Supplement G.	In patients with NYHA class II–IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm (203).	NEW: New data demonstrate a signal of harm when adaptive servo-ventilation is used for central sleep apnea.

- The results of the SERVE-HF trial indicate harm from ASV therapy for CSA – increase in all cause mortality and cardiovascular mortality

Transvenous phrenic nerve stimulation for the treatment of central sleep apnea in heart failure



Transvenous phrenic nerve stimulation for the treatment of central sleep apnoea in heart failure

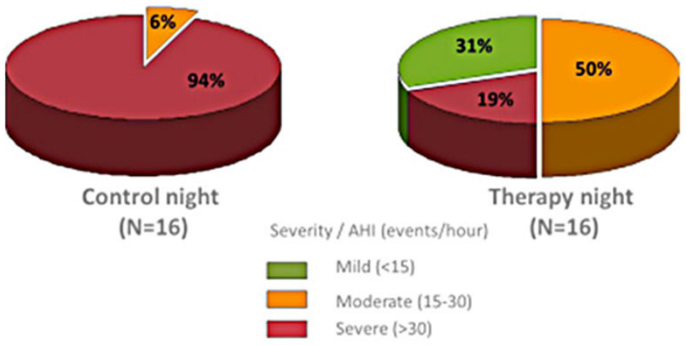
Piotr Ponikowski ✉, Shahrokh Javaheri, Dariusz Michalkiewicz, Bradley A. Bart, Danuta Czarnecka, Marek Jastrzebski, Aleksander Kusiak, Ralph Augostini, Dariusz Jagielski, Tomasz Witkowski, ... Show more

European Heart Journal, Volume 33, Issue 7, 1 April 2012, Pages 889–894,
https://doi.org/10.1093/eurheartj/ehr298
Published: 19 August 2011 **Article history** ▾

See Figure 1 - in the following Journal article for more information:
European Heart Journal, Volume 33, Issue 7, 1 April 2012, Pages 889–894

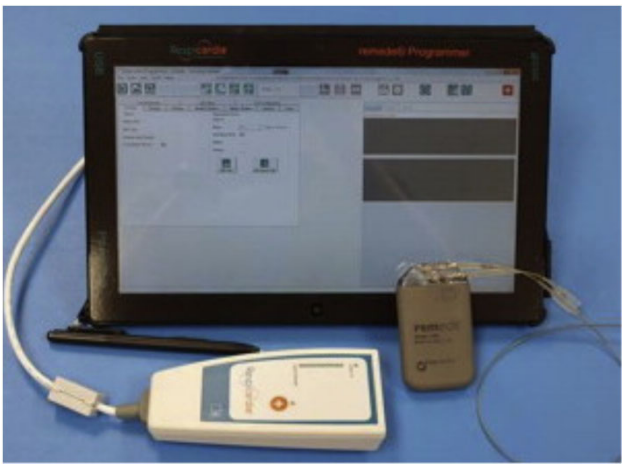
Elimination of respiratory instability and improvement in oxygenation during unilateral phrenic nerve stimulation in a heart failure patient with central sleep apnoea.

Transvenous phrenic nerve stimulation for the treatment of central sleep apnea in heart failure



- Elimination of respiratory instability and improvement in

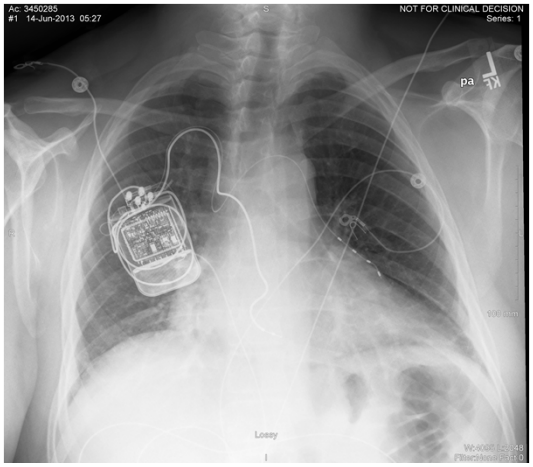
Phrenic Nerve Stimulation for the Treatment of Central Sleep Apnea

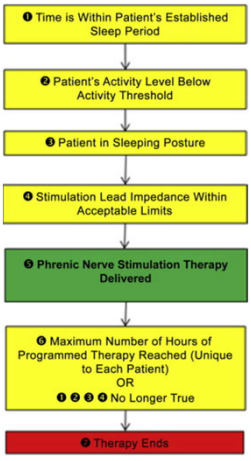


- The remedē System consists of an implantable pulse generator an implantable stimulation leads and an external system programmer.

JACC: Heart Failure May 2015, 3 (5) 360-369

Phrenic Nerve Stimulation for the Treatment of Central Sleep Apnea





The device is implanted in the right pectoral area. The right subclavian approach was used to place the stimulation lead (A) in the left pericardiophrenic vein and to place the sensing lead (B) in the azygos vein.

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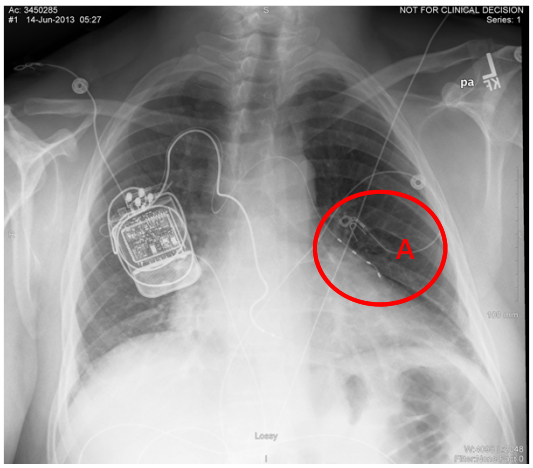

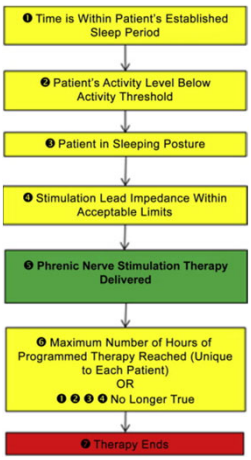

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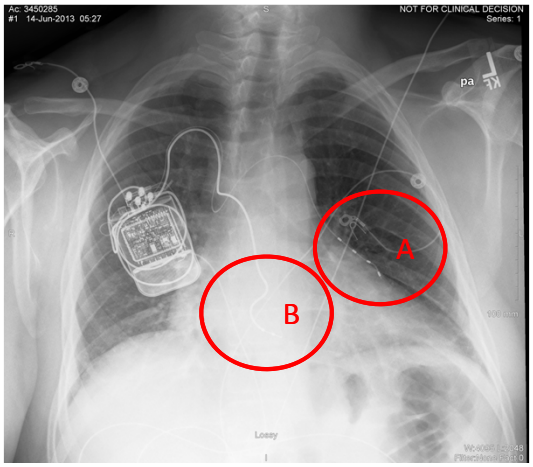

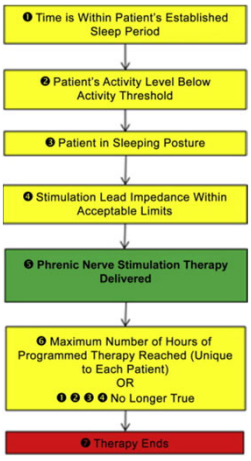

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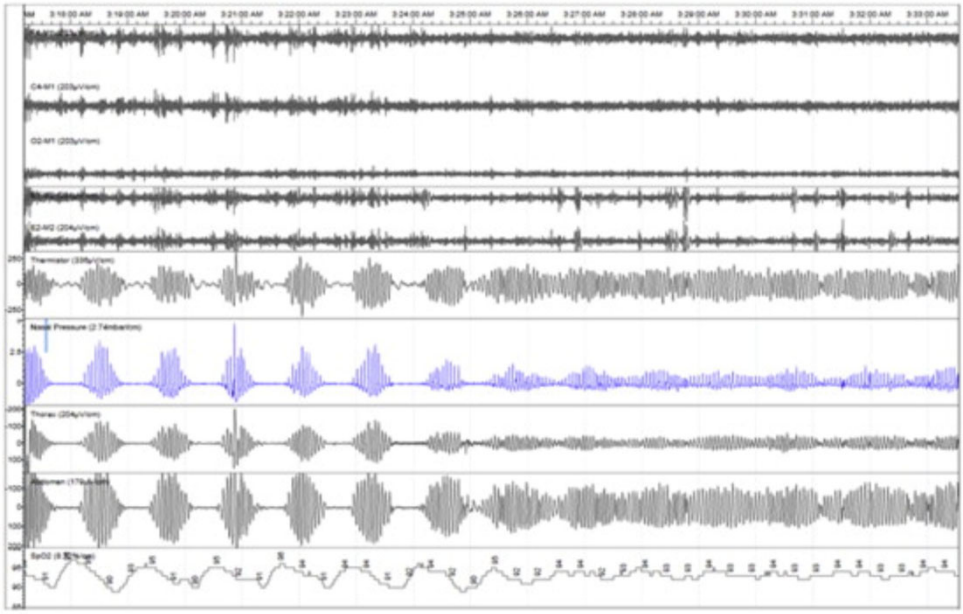

Therapy OFF

Therapy ON

JACC: Heart Failure May 2015, 3 (5) 360-369;

Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial

*Maria Rosa Costanzo, Piotr Ponikowski, Shahrokh Javaheri, Ralph Augostini, Lee Goldberg, Richard Holcomb, Andrew Kao, Rami N Khayat, Olaf Oldenburg, Christoph Stellbrink, William T Abraham, for the remedé System Pivotal Trial Study Group**

- Prospective, multi-center, randomized controlled trial
- AHI > 20 events/hour with at least 50% central events
- 151 eligible patients randomized (1:1) to treatment or control groups at time of implant
  - Control - device implantation but stimulation off for 6 months, then therapy turned on
  - Treatment – device implantation but stimulation programmed on at 1 month post implant

Baseline Characteristics

	Treatment (n=73)	Control (n=78)	Pooled (n=151)
Age (years)	65 (12)	65 (13)	65 (13)
Male	63 (86%)	72 (92%)	135 (89%)
White	70 (96%)	74 (95%)	144 (95%)
Body-mass index (kg/m²)	30·8 (5·3)	31·3 (6·6)	31·1 (6·0)
Neck width (cm)*	42 (5)	43 (5)	42 (5)
Heart rate (beats per min)	75·4 (12·6)	72·9 (13·8)	74·1 (13·3)
Systolic blood pressure (mm Hg)	125·3 (18·3)	123·7 (17·7)	124·5 (17·9)
Diastolic blood pressure (mm Hg)	74·4 (10·5)	75·3 (11·4)	74·9 (11·0)
Respiration rate (breaths per min)	17·5 (2·9)	17·3 (2·6)	17·4 (2·7)
Apnoea-hypopnoea index (events per h)	48·8 (19·3)	43·7 (16·8)	46·2 (18·2)
Central apnoea index (events per h)	30·0 (18·0)	26·6 (16·1)	28·2 (17·1)
Obstructive apnoea index (events per h)	2·6 (3·2)	2·3 (2·7)	2·4 (3·0)
Mixed apnoea index (events per h)	3·1 (4·1)	2·2 (3·3)	2·6 (3·7)
Hypopnoea index (events per h)	13·1 (11·2)	12·7 (11·6)	12·9 (11·4)
ODI4 (events per h)	43·2 (21·7)	37·5 (17·5)	40·2 (19·8)

Lancet. 2016 Sep 3;388(10048):974-82

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Heart rate (beats per min)	75·4 (12·6)	72·9 (13·8)	74·1 (13·3)
Systolic blood pressure (mm Hg)	125·3 (18·3)	123·7 (17·7)	124·5 (17·9)
Diastolic blood pressure (mm Hg)	74·4 (10·5)	75·3 (11·4)	74·9 (11·0)
Respiration rate (breaths per min)	17·5 (2·9)	17·3 (2·6)	17·4 (2·7)
Central apnoea index (events per h)	30·0 (18·0)	26·6 (16·1)	28·2 (17·1)
Obstructive apnoea index (events per h)	2·6 (3·2)	2·3 (2·7)	2·4 (3·0)
Mixed apnoea index (events per h)	3·1 (4·1)	2·2 (3·3)	2·6 (3·7)
Hypopnoea index (events per h)	13·1 (11·2)	12·7 (11·6)	12·9 (11·4)
ODI4 (events per h)	43·2 (21·7)	37·5 (17·5)	40·2 (19·8)

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Baseline Characteristics

	Treatment (n=73)	Control (n=78)	Pooled (n=151)
Age (years)	65 (12)	65 (13)	65 (13)
Male	63 (86%)	72 (92%)	135 (89%)
White	70 (96%)	74 (95%)	144 (95%)
Body-mass index (kg/m²)	30·8 (5·3)	31·3 (6·6)	31·1 (6·0)
Neck width (cm)*	42 (5)	43 (5)	42 (5)
Heart rate (beats per min)	75·4 (12·6)	72·9 (13·8)	74·1 (13·3)
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ODI4 (events per h)	43·2 (21·7)	37·5 (17·5)	40·2 (19·8)

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Baseline Characteristics

Atrial fibrillation	32 (44%)	32 (41%)	64 (42%)
Left ventricular ejection fraction†	39·7 (12·1)	39·4 (12·2)	39·6 (12·1)
Heart failure‡	48 (66%)	48 (62%)	96 (64%)
NYHA class			
I	6/48 (13%)	12/48 (25%)	18/96 (19%)
II	21/48 (44%)	20/48 (42%)	41/96 (43%)
III	21/48 (44%)	16/48 (33%)	37/96 (39%)
IV	0	0	0
Coronary artery disease	40 (55%)	44 (56%)	84 (56%)
Hypertension	53 (73%)	60 (77%)	113 (75%)
Diabetes	27 (37%)	19 (24%)	46 (30%)
Previous stroke	6 (8%)	6 (8%)	12 (8%)
Renal impairment	17 (23%)	21 (27%)	38 (25%)
Concomitant cardiac devices	31 (42%)	33 (42%)	64 (42%)
Implantable cardioverter-defibrillator	19/31 (61%)	14/33 (42%)	33/64 (52%)
CRT-D	9/31 (29%)	11/33 (33%)	20/64 (31%)
Non-CRT pacemaker	2/31 (6%)	8/33 (24%)	10/64 (16%)
CRT-P	1/31 (3%)	0	1/64 (2%)

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Baseline Characteristics

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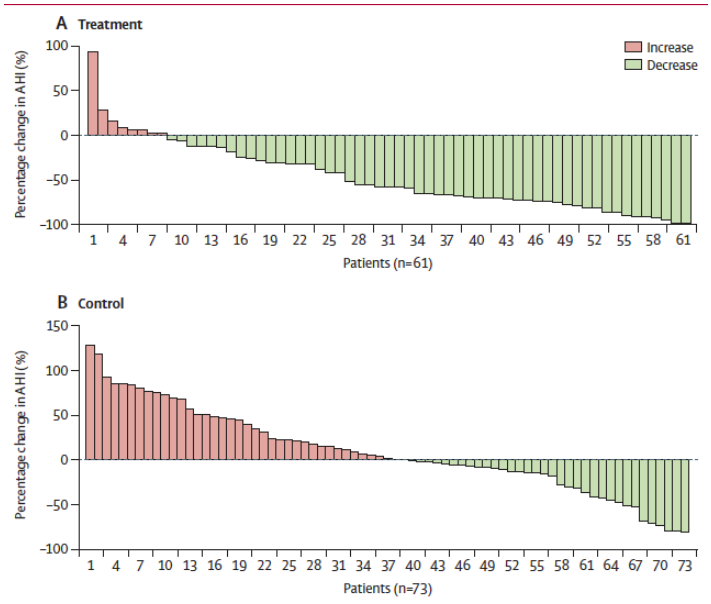
Percent Change in AHI at 6 months



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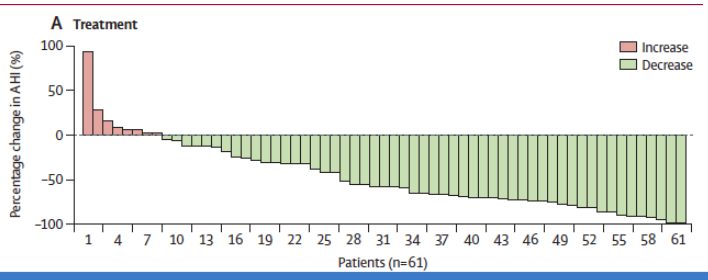
Percent Change in AHI at 6 months



Primary Endpoint Met:

- The proportion of subjects achieving ≥50% reduction in AHI for the Treatment group was **51%** compared to **11%** for the Control group, resulting in a difference between groups of **41%** in favor of the Treatment group (p<.0001)
- **87%** of patients in the Treatment Group had a reduction in AHI at 6 months

Patients (n=73)

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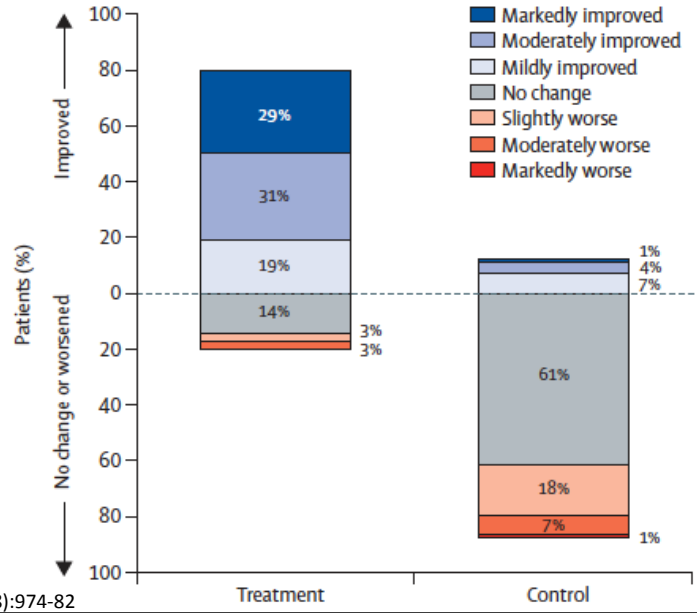
Percent Change in AHI at 6 months



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Safety and Feasibility

	Treatment (n=73)	Control (n=78)
Any event	6 (8%)	7 (9%)
Investigational device implant		
Impending pocket erosion	1 (1%)	1 (1%)
Implant site haematoma	0	1 (1%)
Implant site infection	2 (3%)	0
Investigational device system		
Extra-respiratory stimulation	1 (1%)	0
Concomitant device interaction	1 (1%)	0
Lead component failure	0	1 (1%)
Lead dislodgement	0	2 (3%)
Lead displacement	1 (1%)	0
General disorders and site conditions		
Non-cardiac chest pain	0	1 (1%)
Abnormal laboratory values		
Elevated transaminase	0	1 (1%)

***Table 3*: Serious adverse events associated with procedure, device, or therapy at 12 months' follow-up**

Implant Metrics:

- 97% implant success rate
- 3.4% lead revision rate
- 2.7 +/- 0.8 hours ave. implant time
- No deaths related to procedure or therapy

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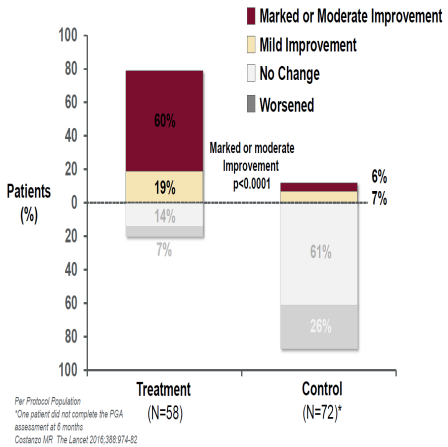
Improvements in Quality of Life

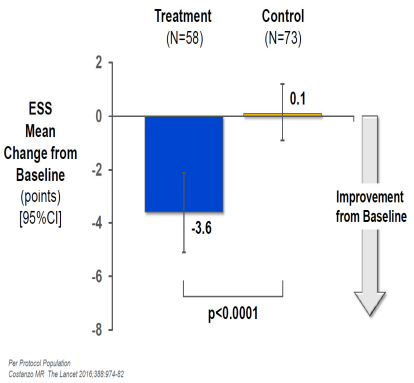
Patient Global Assessment

79% of Patients with Improved QoL

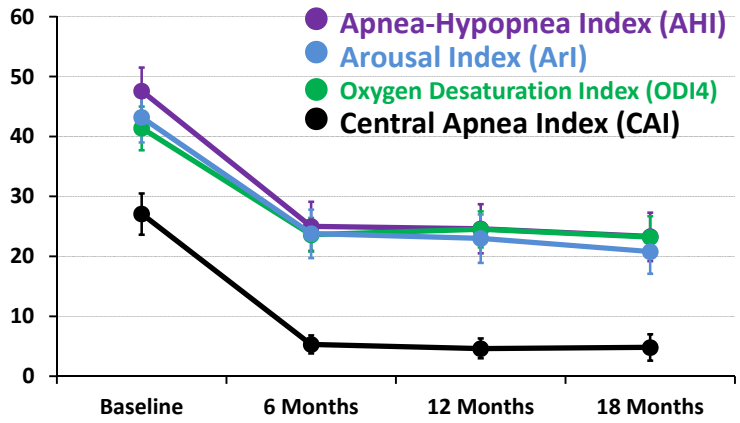


Epworth Sleepiness Scale

Reduction of 3.6 Points with Treatment

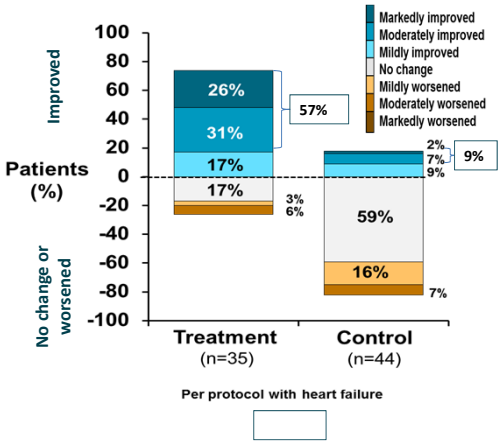


Sleep Improvements Sustained Over Time



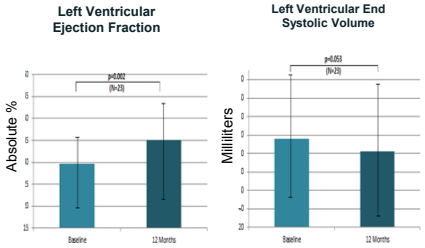
Heart Failure Patients Demonstrate Similar Benefit in Sleep and Quality of Life

- Post-hoc analysis showed between Group improvements
  - **Sleep metrics** *(All p<0.0001)*
    - Apnea Hypopnea Index (AHI)
    - Central Apnea Index (CAI)
    - Oxygen Desaturation Index (ODI)
    - Arousal Index
  - **Epworth Sleepiness Scale**
    - 3.2 ± 4.9 point improvement between groups *(p=0.001)*
  - **Patient Global Assessment**
    - 57% vs 9% (p<0.0001; Figure)

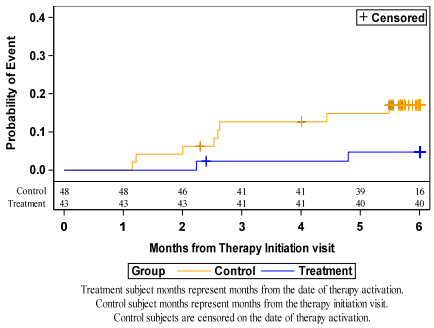


Post-hoc Heart Failure Analysis Demonstrates Improvements in Heart Failure Specific Metrics

- Minnesota Living with Heart Failure improved by 6.3±17.0 points (baseline to 12 months; p=0.044; n=32)
- Improvement in left ventricular ejection fraction and remodeling



- Trend towards a decrease in **time to first HF hospitalization**



Summary

- Central sleep apnea (CSA) is caused by an intermittent neural drive to breathe resulting in a periodic breathing pattern. It is prevalent in 30-50% of heart failure patients as well as patients with atrial fibrillation and stroke.
- Central sleep apnea is an independent predictor of mortality and heart failure rehospitalization.
- In the Pivotal trial of the remede® system, 87% of patients in the Treatment Group had a reduction in AHI at 6 months, with 29% experiencing marked improvement and 31% experiencing moderate improvement in AHI. Results were sustained over 18 months and beyond.
- In the Patient Global Assessment, 79% of patients receiving treatment reported improved quality of life.
- The remede system can be implanted safely in about 2.7 hours

Summary

- A post hoc analysis of the subgroup of heart failure patients in the Pivotal trial indicated that heart failure patients responded well to remede system therapy including:
  - Improved sleep metrics and decreased sleepiness
  - Improvement in MLWHFQ, LVEF, & LV remodeling
  - Decrease in time to first heart failure hospitalization