

Sleep apnea and chronic heart failure

An update on practical aspects
(December 2017)

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Comment — Thank you for inviting me to this meeting



Sleep apnea (SA) and heart failure (HF)

1. Presentation & diagnosis of SA in HF patients

2. Mechanisms that potentially link SA and HF

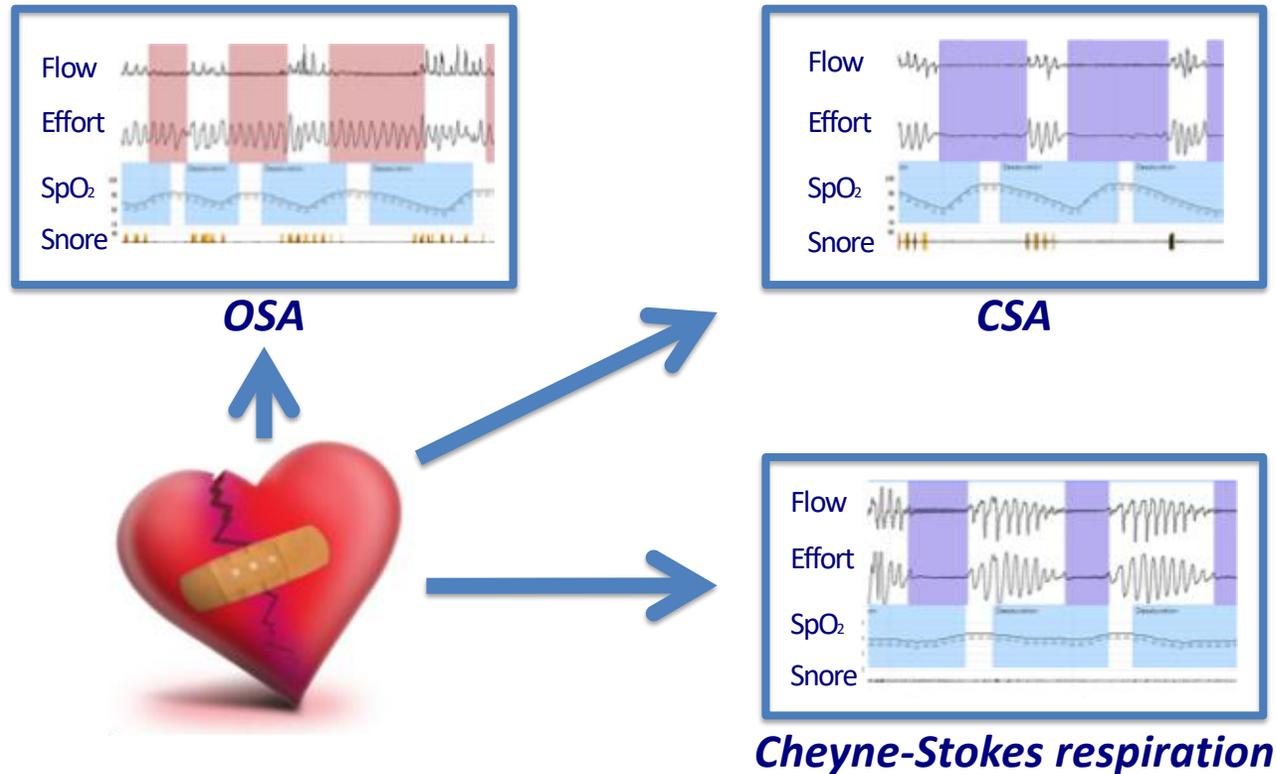
3. Arrhythmias and mortality

4. Effect of **treatment** of one condition on the severity of the other

5. **Conclusion** and perspectives

***Comment** — Sleep apnea is a co-morbidity that might aggravate heart failure. In this 15 min presentation, I will focus on some critical aspects of the link between sleep apnea and heart failure.*

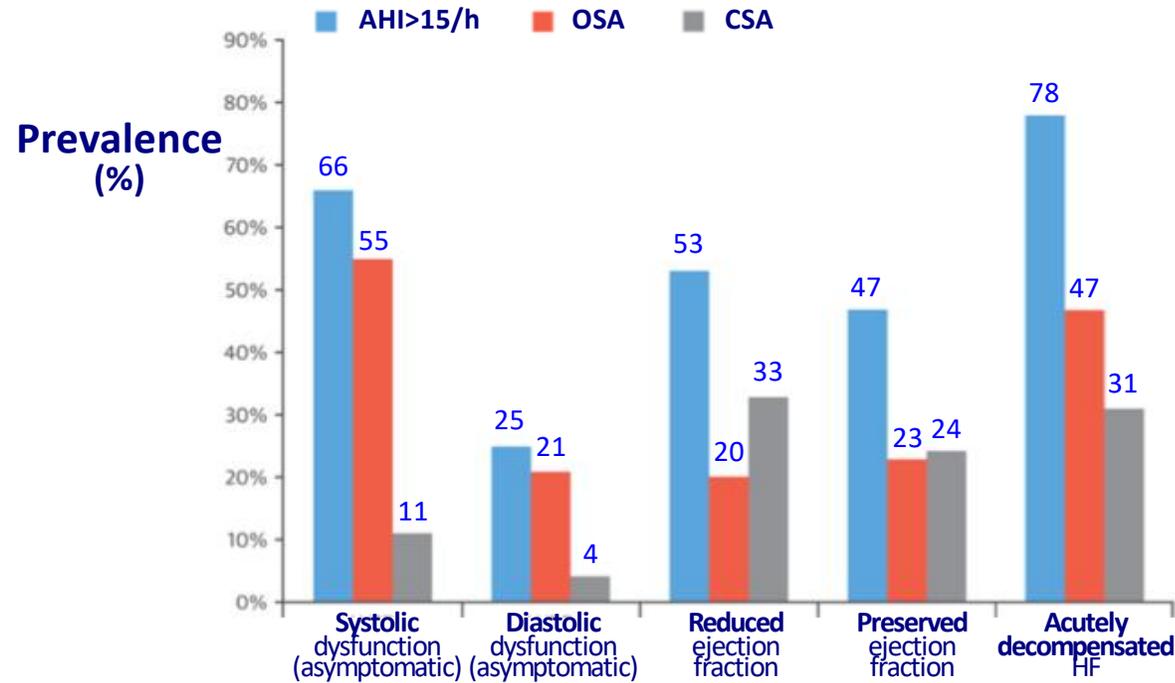
Types of SA in HF patients



Jen et al., Can J Cardiol, 2015, 31, 880-888

Comment — Heart failure patients may not have sleep apnea or may present with obstructive sleep apnea, central sleep apnea, or Cheyne-Stokes respiration. These types of sleep apnea are often associated with one another.

CSA and OSA are prevalent in left ventricular dysfunction



AHI, apnea-hypopnea index

Javaheri et al., JACC, 2017, 69, 841-858

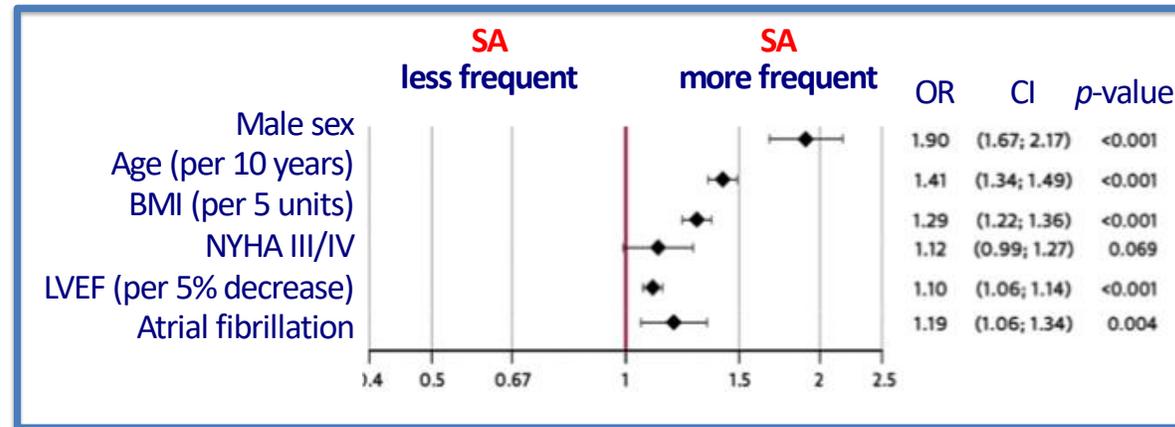
Comment — Heart failure can have any of the following presentations:

- with systolic or diastolic dysfunction, or with a preserved or reduced ejection fraction .
- Sleep apnea is highly prevalent in heart failure patients. The prevalence of each type of apnea, and their severity, are different in each of these categories.
- Please note that the more severe the heart failure is, the more central the sleep apnea is.

Clinical predictors of SA in HF patients

The SchlaHF Registry

N = 6,876 HF patients
46% with moderate-to-severe SA

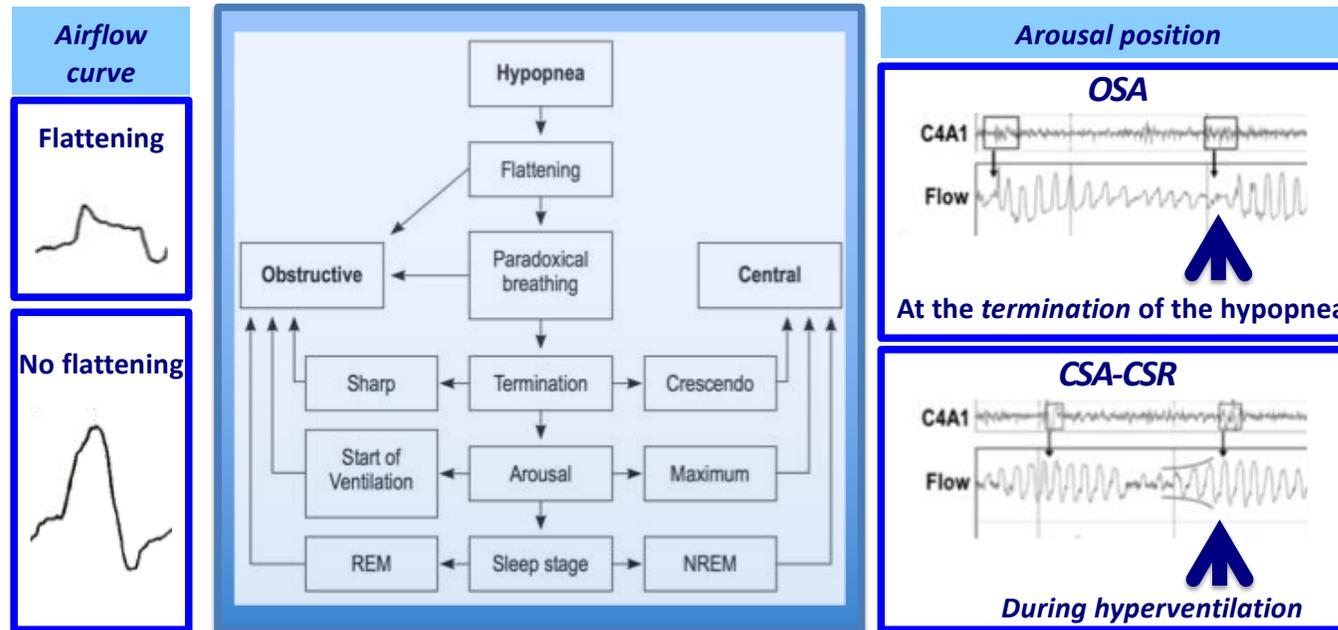


Arzt et al., JACC HF, 2016, 4, 116-125

NYHA: New York Heart Association ; BMI: body mass index;
LVEF: Left ventricle ejection fraction

Comment — Clinical predictors for at least moderate sleep apnea include male sex, older age, higher BMI, higher NYHA functional classification, more severe impairment of systolic cardiac function, and atrial fibrillation. As you can see, none of these predictors is a good predictor. That's why patients with heart failure would systematically benefit from undergoing a sleep study.

Differentiation of obstructive and central hypopneas is of diagnostic, prognostic, and therapeutic importance.



Randerath et al., *Sleep*, 2013, 36, 363-368

Comment — A critical fact to point out is the differentiation between central and obstructive events, because they have varying diagnostic, prognostic, and therapeutic consequences. This algorithm helps to differentiate obstructive from central hypopneas. Flattening of the inspiratory airflow curve, arousal position, paradoxical breathing, sleep stages, and the breathing pattern at the end of the hypopnea can each give helpful clues for the classification of hypopnea.



SA and HF

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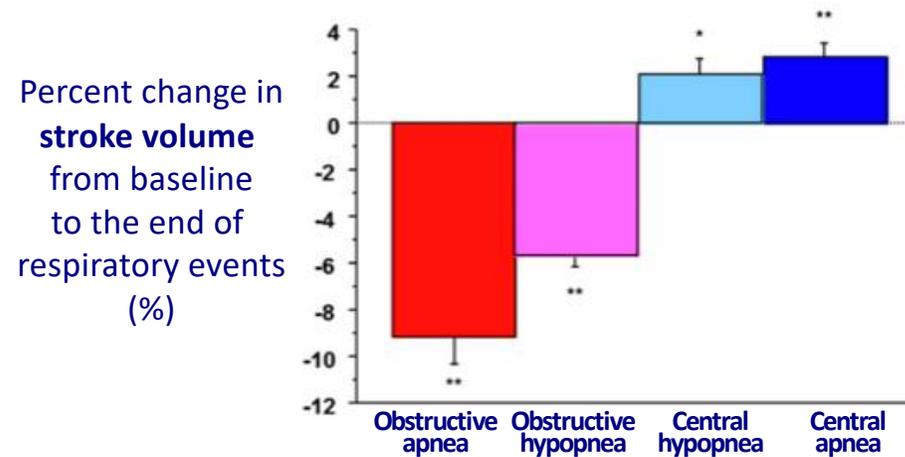
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Comment — Let's examine some mechanisms potentially linking sleep apnea and heart failure.

Differing effects of OSA and CSA on *stroke volume* in 40 HF patients



Stroke volume was assessed using photoplethysmography

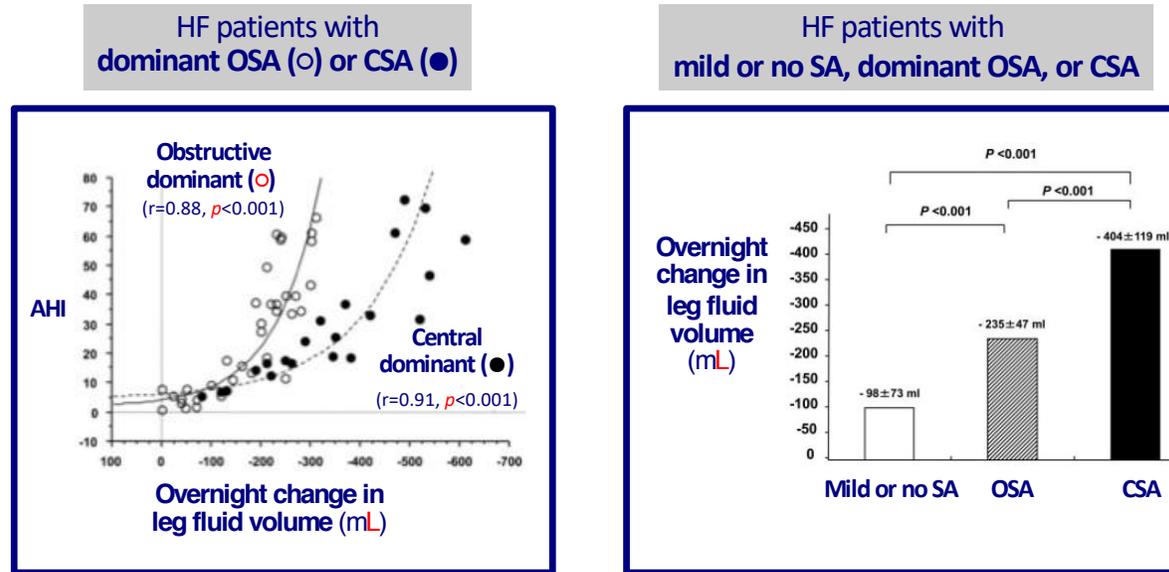
Yumino et al., *AJRCCM*, 2013, 187, 433-438

Comment — *Hemodynamics. Let's focus on the differing effects of OSA and CSA on stroke volume.*

- *During obstructive events, stroke volume **decreased**.*
- *During central events, it **increased**.*
- *Similar variations were observed with cardiac output.*

*Obstructive sleep apnea appeared to have **adverse hemodynamic effects**, whereas central sleep apnea appeared to have little or slightly positive hemodynamic effects in this study.*

HF may contribute to causation of SA



The **overnight change** in leg fluid volume was measured before and after polysomnography.

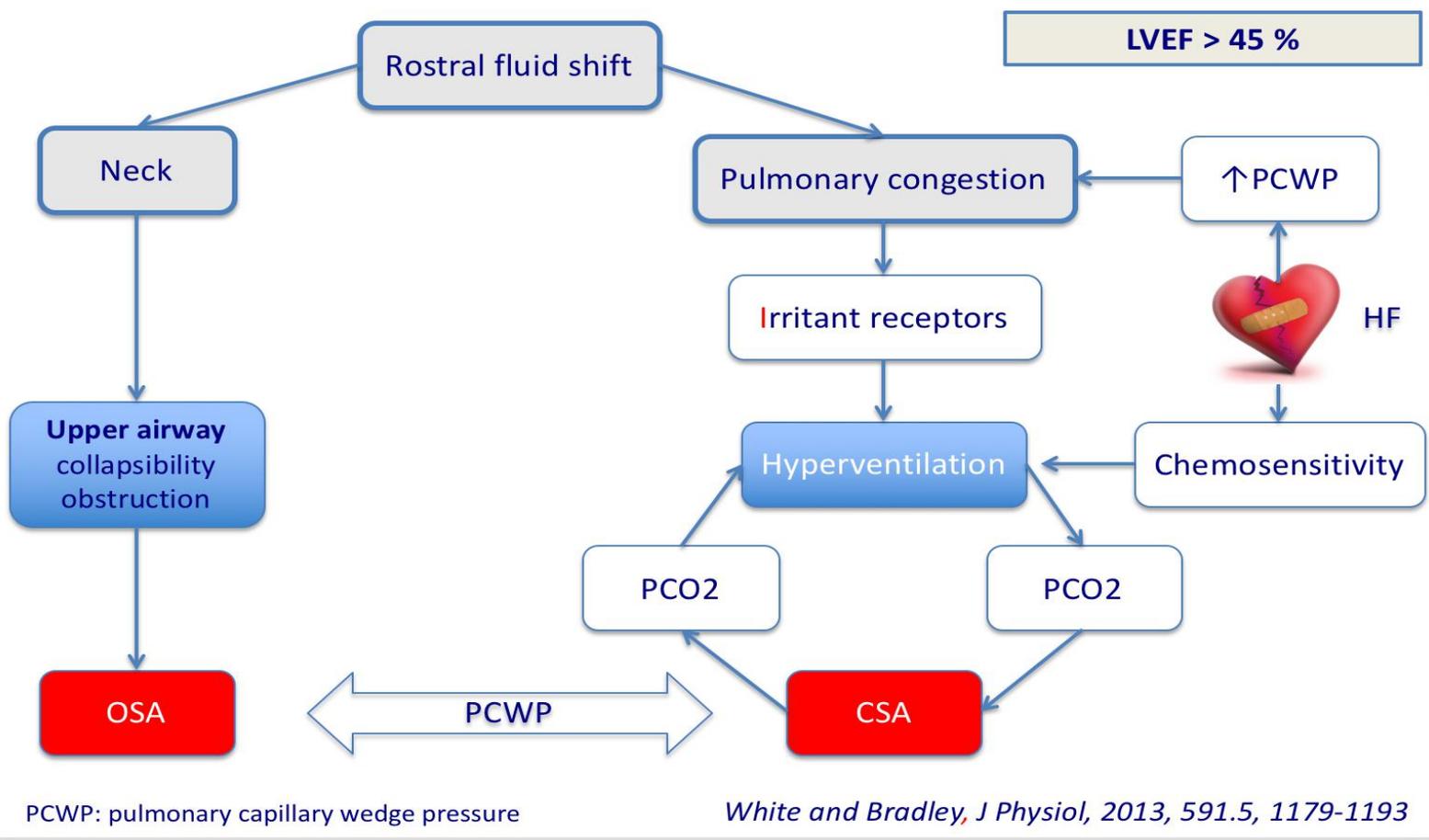
Yumino et al., *Circulation*, 2010, 121, 1598-1605

Comment — This Canadian group showed that the overnight volume of fluid displacement from the legs to the thorax and the neck may contribute to aggravation of sleep apnea. In this study, heart failure patients were divided into 2 groups: those with **obstructive-dominant** sleep apnea and those with **central-dominant** sleep apnea.

- In both groups of patients, the overnight change in leg fluid volume correlated independently with the AHI.
- Moreover, the greater the volume of fluid displacement from the legs to the thorax and the neck, the higher the probability of **central-dominant** sleep apnea.

This means that the magnitude of overnight rostral fluid movement contributed not only to the severity of sleep apnea, but also to its predominant type.

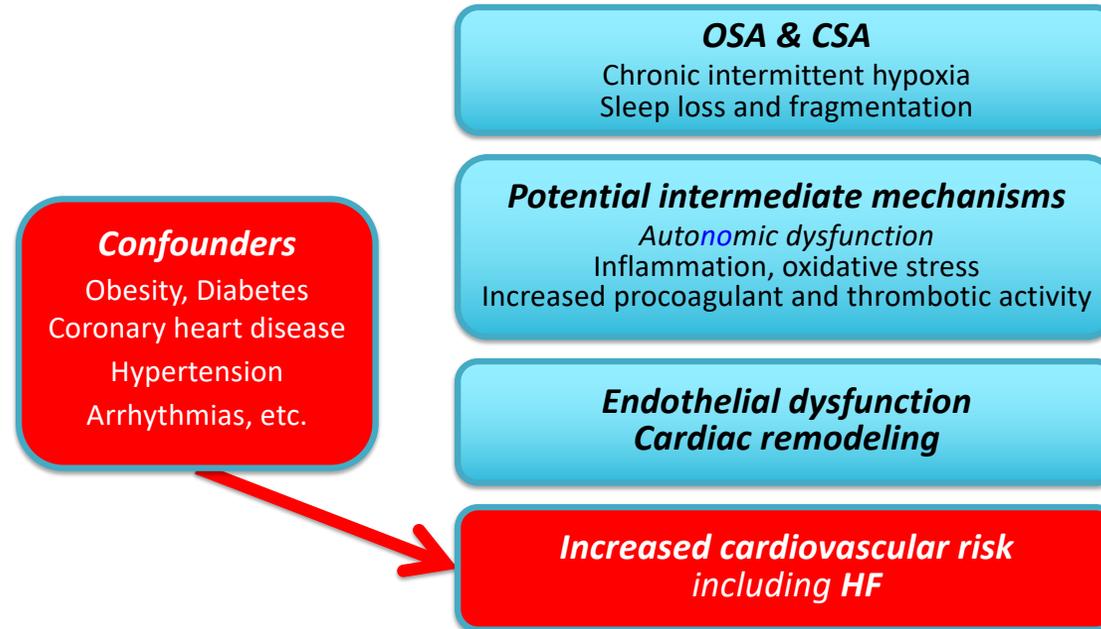
The role of overnight rostral fluid shift in the pathogenesis of OSA and CSA



Comment — There might be interplay between overnight fluid shift and the development of OSA and CSA.

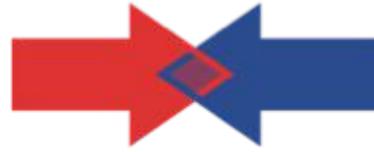
- Overnight fluid shift from the legs to the neck can **affect upper airway mechanics** and lead to **OSA**.
- Fluid shift to the **lungs** can provoke **hyperventilation, hypocapnia, and CSA**

SA might contribute to the development and/or aggravation of HF



Comment — *Sleep apnea may contribute to the development and/or aggravation of heart failure.*

- *Very briefly, the repeated episodes of apnea, hypoxia/reoxygenation, and arousal throughout the night are factors that lead to the pathophysiologic consequences of sleep apnea; all may contribute to worsening heart failure.*
- *Please note that sleep apnea comorbidities are confounders that are able to produce **similar** cardiovascular damage. This makes it difficult to discern whether it is the sleep apnea or the confounders that are the root cause of the cardiovascular complications associated with sleep apnea.*



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Comment — Let us now focus on 2 potential severe adverse effects of sleep apnea in heart failure patients – arrhythmias and mortality.

Atrial fibrillation in HF patients with CSA

Incident atrial fibrillation		Incident HF	
Predictors	Multivariable adjusted OR (95% CI)	Predictors	Multivariable adjusted HR (95% CI)
CAI < 5	1.00 (reference)	CAI ≥ 5	1.79 (1.16-2.77)
CAI ≥ 5	2.58 (1.18-5.66)	CSA-CSR	2.23 (1.45-3.41)
No CSA-CSR	1.00 (reference)		
CSA-CSR	2.27 (1.13-4.56)		

May et al.,
AJRCCM, 2016, 193, 783-791

Javaheri et al.,
AJRCCM, 2016, 193, 561-568

CAI, central apnea index

N = 2,911 older (>65 y) men
Mean follow-up duration: **6 y**

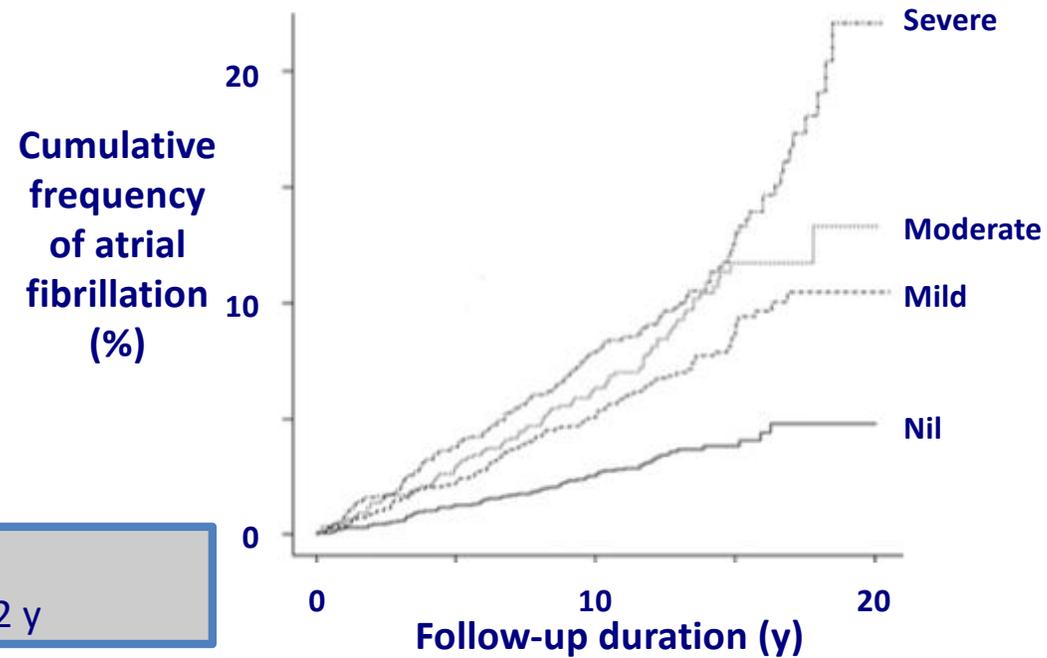
Comment — This slide presents a cohort of patients with CSA and those with CSA and Cheyne-Stokes respiration.

- These patients were associated with an increased risk of atrial fibrillation and incidence of heart failure.
- Conversely, OSA did not predict incidence of atrial fibrillation and was not associated with incidence of heart failure.

Whether CSA is a causative factor for heart failure, or represents an early symptom of HF, is open for speculation.

Atrial fibrillation in HF patients with OSA

Predictor for incident atrial fibrillation	HR (95% CI)	<i>p</i>
AHI>5	1.55 (1.21-2.00)	<0.001

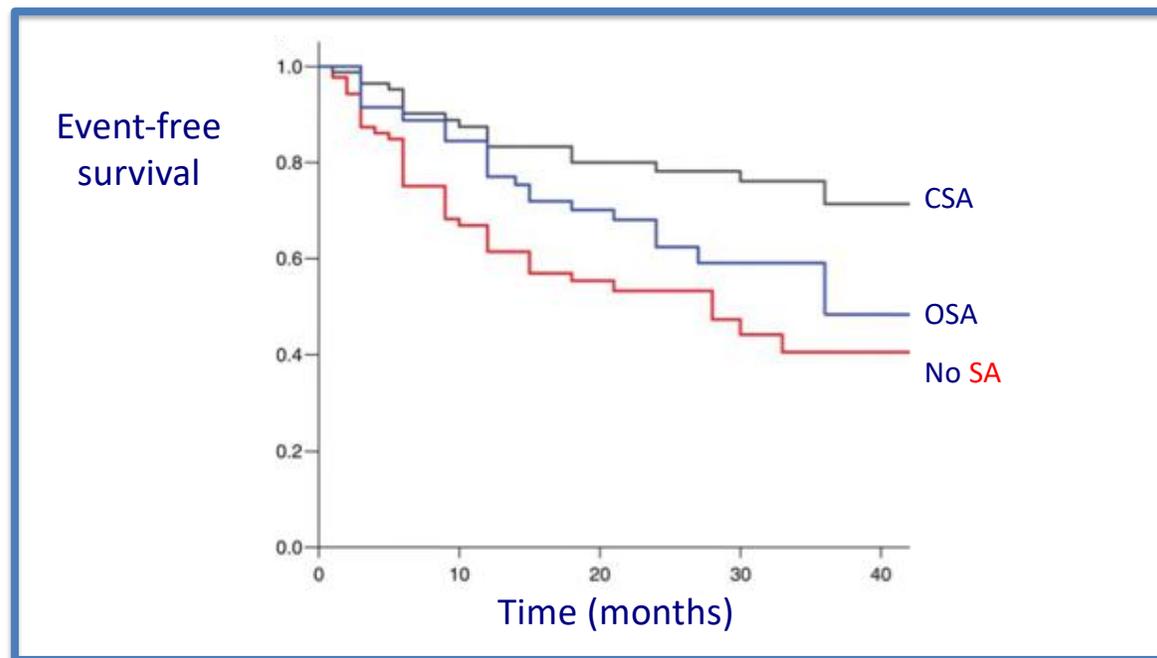


N = 6,841
Follow-up duration: 12 y

Cadby et al., Chest, 2015, 148, 945-952

Comment — On the contrary, in this large follow-up study, OSA diagnosis and severity were independently associated with incidence of atrial fibrillation.

Ventricular arrhythmias in 472 HF patients with SA



CSA HR 2.15, 95% CI 1.40-3.30, $p < 0.001$

OSA HR 1.69, 95% CI 1.64-1.75, $p = 0.001$

Bitter et al., Eur Heart J, 2011, 32, 61-74

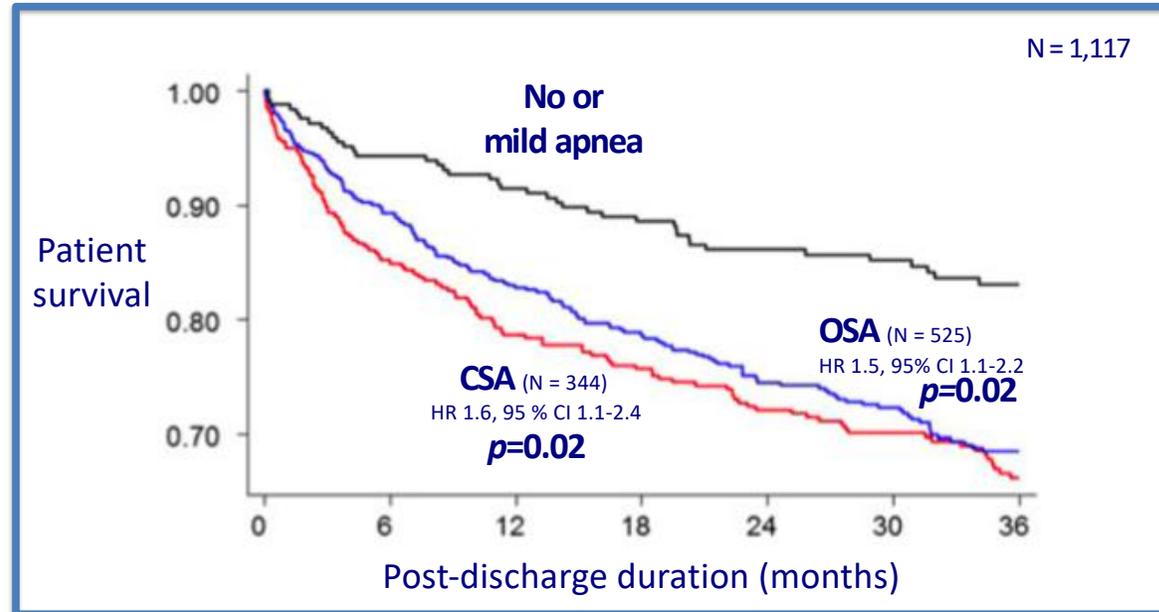
Comment — Here, heart failure patients were screened for OSA and CSA after implantation of a cardiac resynchronization device with cardioverter-defibrillator.

OSA and CSA were associated with an increased independent risk of ventricular arrhythmias. This increased risk was also recently recognized in a European Task Force report.

Mortality

Post-discharge survival plot of acute HF patients

— a prospective study —



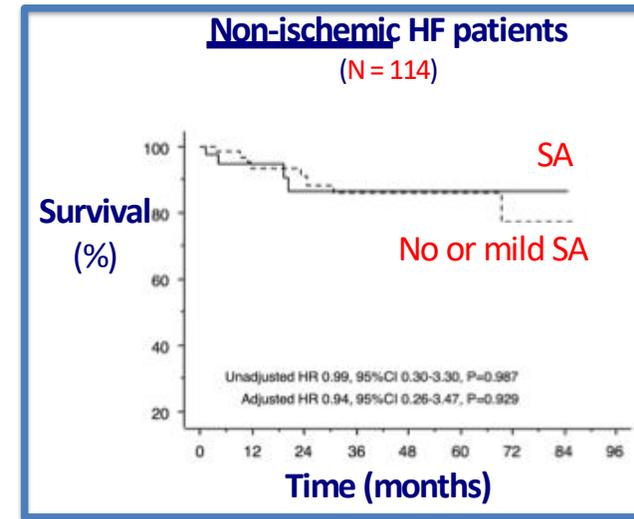
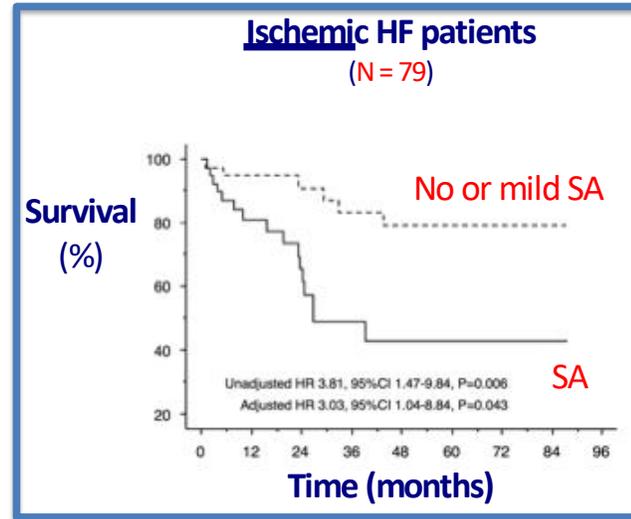
HR: hazard ratio; CI: confidence interval

Khayat et al., Eur Heart J, 2015, 36, 1463-1469

Comment — Increased mortality rates were reported in both OSA patients and CSA patients compared to those without sleep apnea in this study that followed patients post-discharge after acute heart failure. In other studies with fewer participants, CSA, but not OSA, was associated with higher mortality in HF patients.

Mortality

SA and mortality in ischemic HF



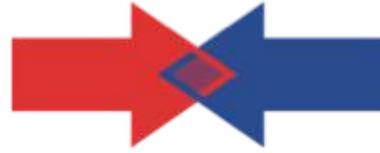
% central events:

Ischemic patients: 55±38

Non-ischemic patients: 44±38

Yumino et al., Heart, 2009, 95, 819-824

- Comment** — In this study, heart failure patients were divided into those with ischemic and those with non-ischemic cardiomyopathy.
- In the ischemic group only, mortality was significantly higher in those with sleep apnea than in those without sleep apnea.
 - Patients with ischemic heart failure may be more susceptible to the adverse effects of sleep apnea.

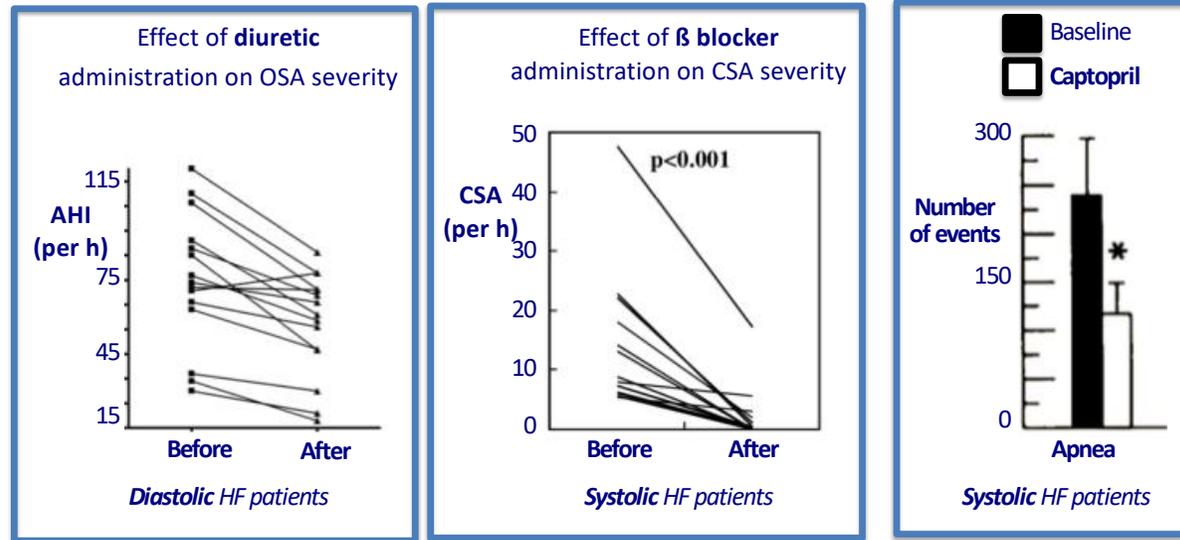


SA and HF

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- 4. Effect of treatment of one condition on the severity of the other**
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***Comment** — Let's now examine the effect of treatment of either condition on the severity of the other*

Optimal HF treatment and SA severity



Bucca et al., *Chest*, 2007,
132, 440-446

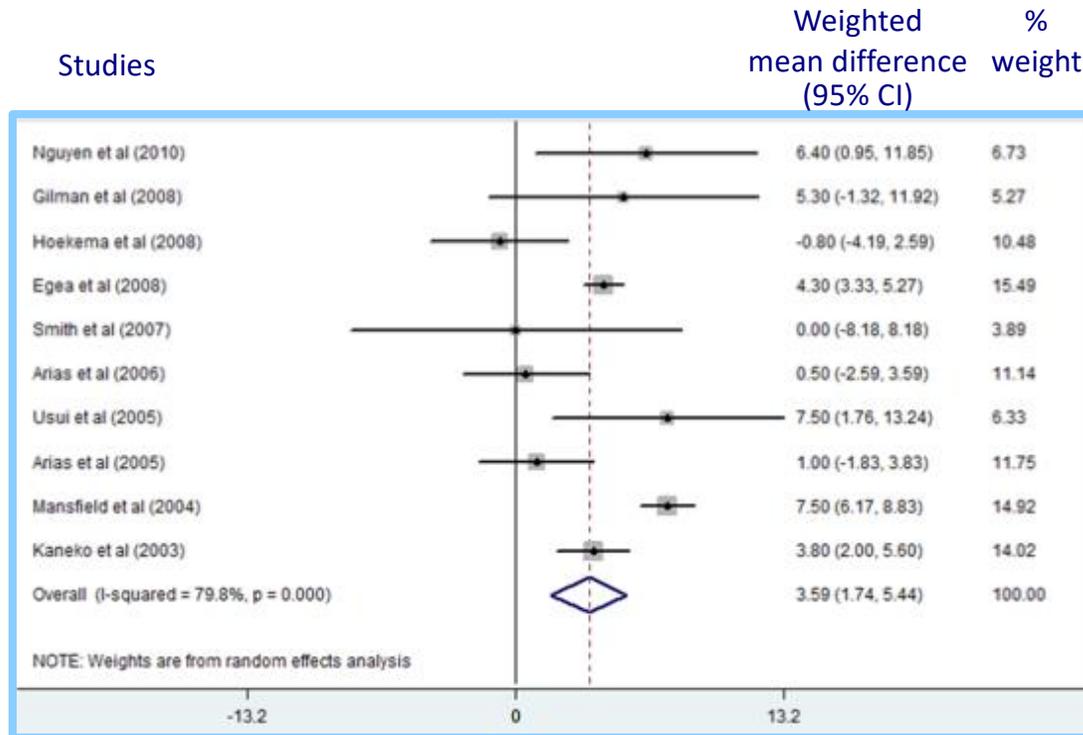
Tamura et al., *Circ J*, 2009,
73, 295-298

Walsh et al., *Br Heart J*,
1995, 73, 237-241

Comment — The first step in the management of sleep apnea with concurrent heart failure is optimization of the heart failure treatment.

- Some studies have reported a significant effect of heart failure therapy on sleep apnea severity.
- Administration of diuretic was shown to improve OSA in HF patients with hypervolemia.
- Captopril and beta-blockers reduced CSA.

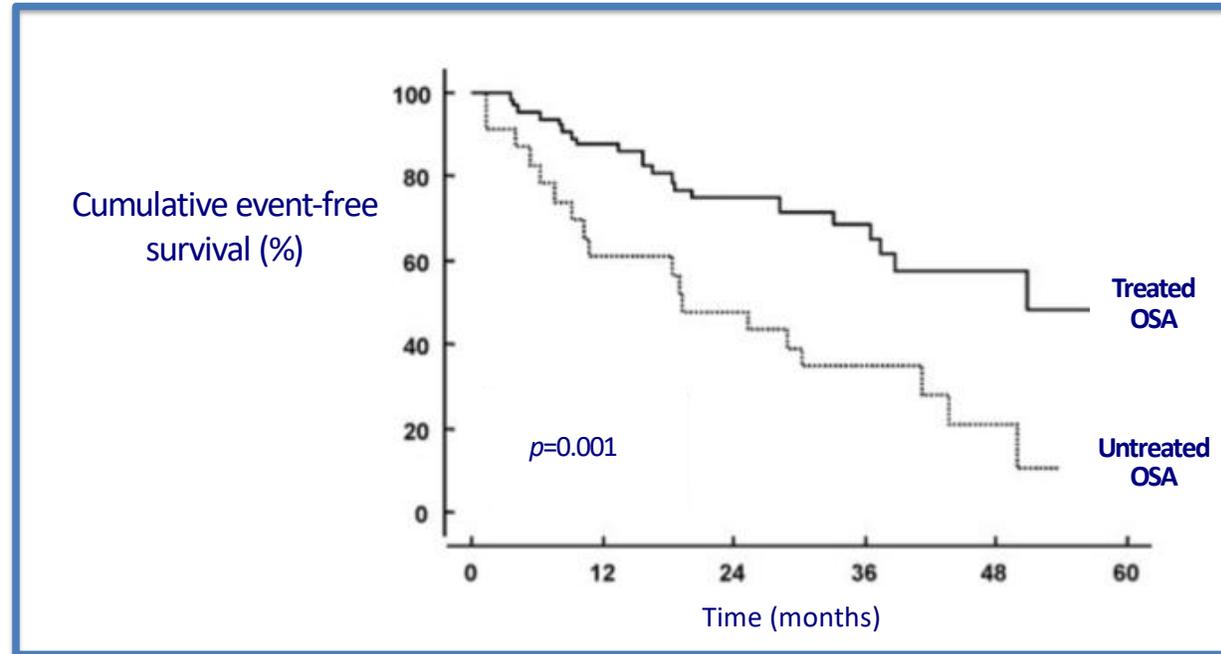
CPAP administration improves left ventricular ejection fraction (LVEF) in HF patients with OSA



Sun et al., PLoS One, 2013, 8, e62298

Comment — This is the result of a meta-analysis of RCT studies that showed a significant improvement in LVEF after CPAP treatment in heart failure patients with OSA.

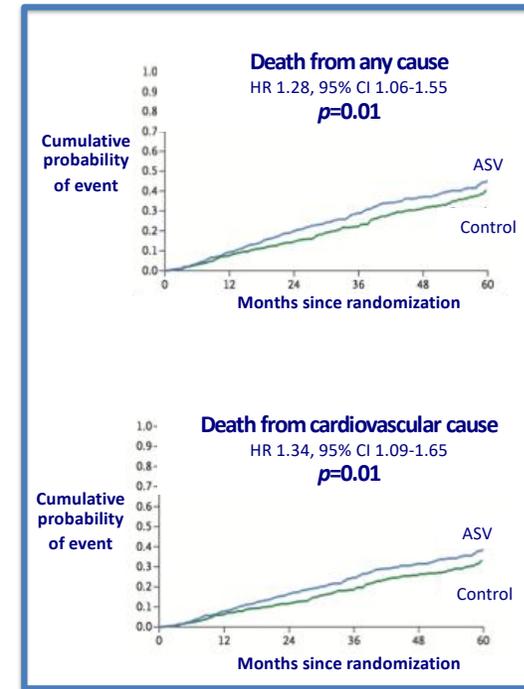
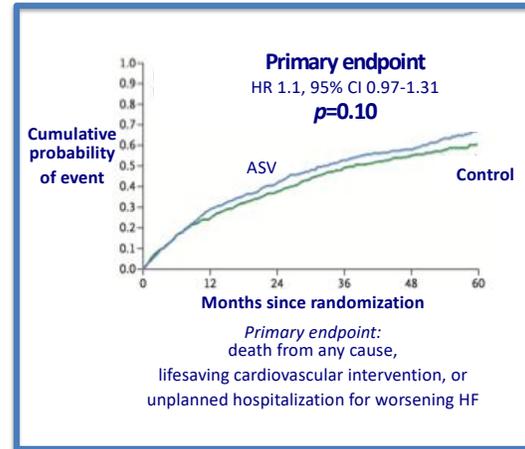
Effect of **OSA** treatment on **mortality** and morbidity in HF patients



Kasai et al., Chest, 2008, 133, 690-696

Comment — In this non-randomized study including 88 HF patients with OSA, hospitalization-free survival was significantly greater in the 65 CPAP-treated patients than in the 23 untreated patients over 2.1 years. Unfortunately, these results are not conclusive due to the non-randomized nature of the study and its small sample size.

Adaptive servo-ventilation (ASV) for CSA in systolic HF (LVEF<45%): *The SERVE study*



Cowie et al., *NEJM*, 2015, 373, 1095-1105

Comment — This important study investigated the effects of adaptive servo-ventilation in heart failure patients with reduced ejection fraction below 45% and predominantly CSA.

- The primary endpoint was a composite of these variables. There was no difference between the ASV group and the control group.
- For the endpoints **death from any cause** and **death from cardiovascular cause**, there was an increase in mortality in the ASV-treated group that seemed to occur early.

Therefore, treating patients with ejection fraction <45% with ASV is deleterious.

There is currently no explanation in terms of pathophysiology.

Task force report ERS statement

TASK FORCE REPORT
ERS STATEMENT

Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep

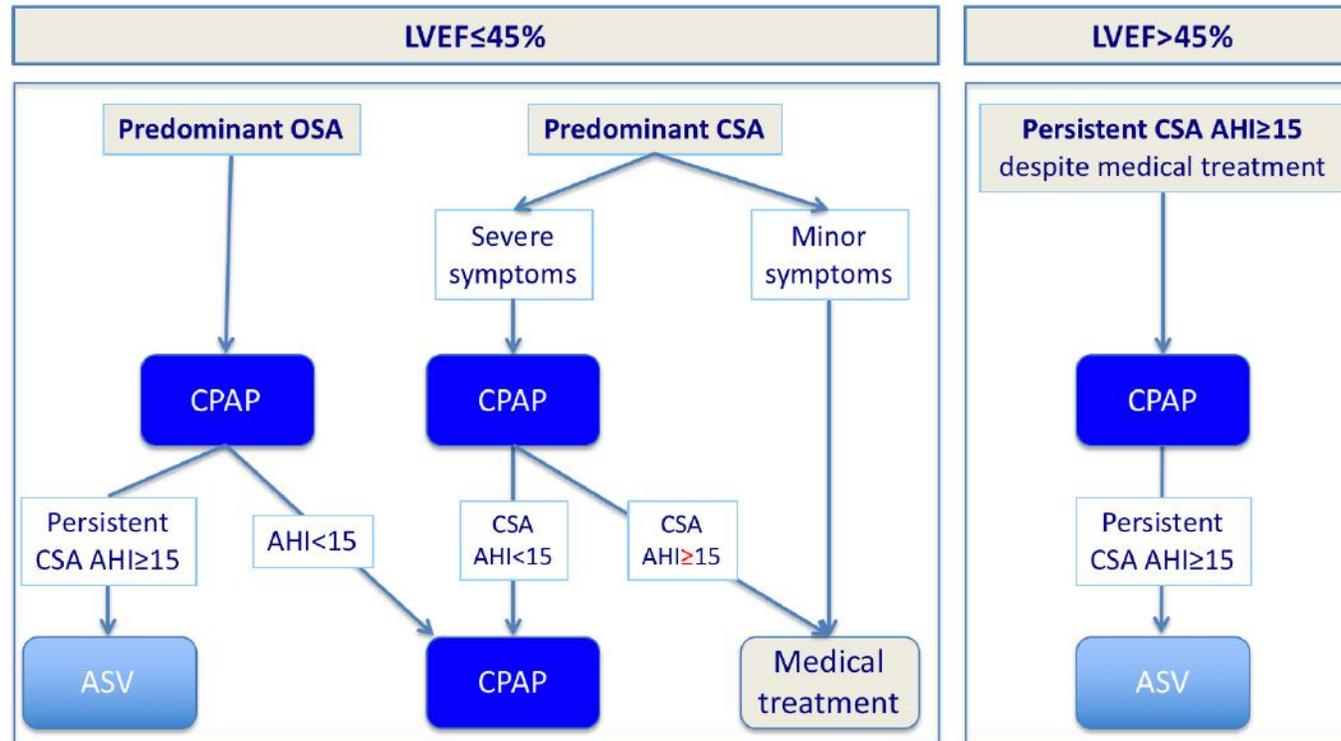
Winfried Randerath^{1,21,22}, Johan Verbraecken^{2,21,22}, Stefan Andreas^{3,4}, Michael Arzt⁵, Konrad E. Bloch⁶, Thomas Brack⁷, Bertien Buyse⁸, Wilfried De Backer², Danny Joel Eckert⁹, Ludger Grote¹⁰, Lars Hagmeyer¹, Jan Hedner¹⁰, Poul Jennum¹¹, Maria Teresa La Rovere¹², Carla Miltz¹, Walter T. McNicholas¹³, Josep Montserrat¹⁴, Matthew Naughton¹⁵, Jean-Louis Pepin¹⁶, Dirk Pevernagie¹⁷, Bernd Sanner¹⁸, Dries Testelmans¹⁸, Thomy Tonia¹⁹, Bart Vrijsen⁸, Peter Wijkstra²⁰ and Patrick Levy^{16,22}

Randerath et al., Eur Respir J, 2017, 49, 1600959

Comment — *To begin the conclusion of my presentation, I will summarize a recently published European Task force report.*

Conclusion — Treatment of SA in patients with *optimally treated HF and cardiovascular risks*

Randerath et al., Eur Respir J, 2017, 49, 1600959



Comment — In heart failure patients, sleep apnea is systematically assessed.

- Optimization of medical heart failure treatment is the first step in the management of sleep apnea.
- The decision tree takes into account the level of ejection fraction (lower or greater than 45%), and the type of dominant sleep apnea (obstructive or central).
- Please note that the first line of treatment recommended, if any, is CPAP administration.
- If ejection fraction is >45% and CSA persists, treatment shifts to ASV administration.
- Conversely, if ejection fraction is less than or equal to 45%, and the AHI decreases below 15, CPAP can be continued.
- If the AHI remains at 15 or greater, it is suggested to discontinue CPAP treatment. If there are minor symptoms, the report suggests to not administer CPAP treatment.



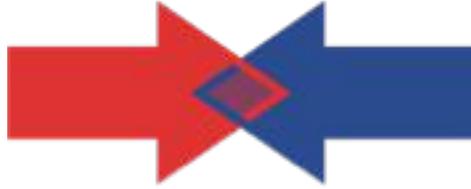
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Comment — *Our understanding of the pathophysiology of the link between sleep apnea and heart failure has improved in the last 2 decades.*

- *Studies suggest that sleep apnea and heart failure might have a dangerous association due to the increased risk of arrhythmias and the excessive mortality rates in patients with both conditions.*
- *In practice, assessment and treatment of sleep apnea and heart failure require a precise description of the clinical situation and of polysomnographic pattern.*
- *Optimization of medical heart failure treatment is the first step in the management of sleep apnea.*
- *OSA is thought to contribute to heart failure, and therefore, it should be diagnosed and treated independent of heart failure.*
- *The role of adaptive servo-ventilation remains speculative until more data become available. You may have noticed that I did not mention transvenous phrenic nerves stimulation, which is also currently highly speculative.*



Thank you

