Sleep Apnea and Cardiovascular Disease

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"Laugh and the world laughs with you, snore and you sleep alone." – Anthony Burgess

Disclosures

- Clinical Manager Sleep and Respiratory Care at Philips SA and EA
- SSEM sponsored

Cardiovascular Physiology Overview

Cardiovascular System Function

1. **Transport**
- Nutrients and O_2
- Remove metabolic byproducts (ADP, K^+, CO_2)
- Hormones
2. **Protection**
- Immune cells, antibodies, complement proteins, coagulation
3. **Regulation**
- Body temperature, pH and fluids

Berne R, Levy M. Cardiovascular Physiology. 8th ed. : Mosby; 2001.

The Heart: Structure

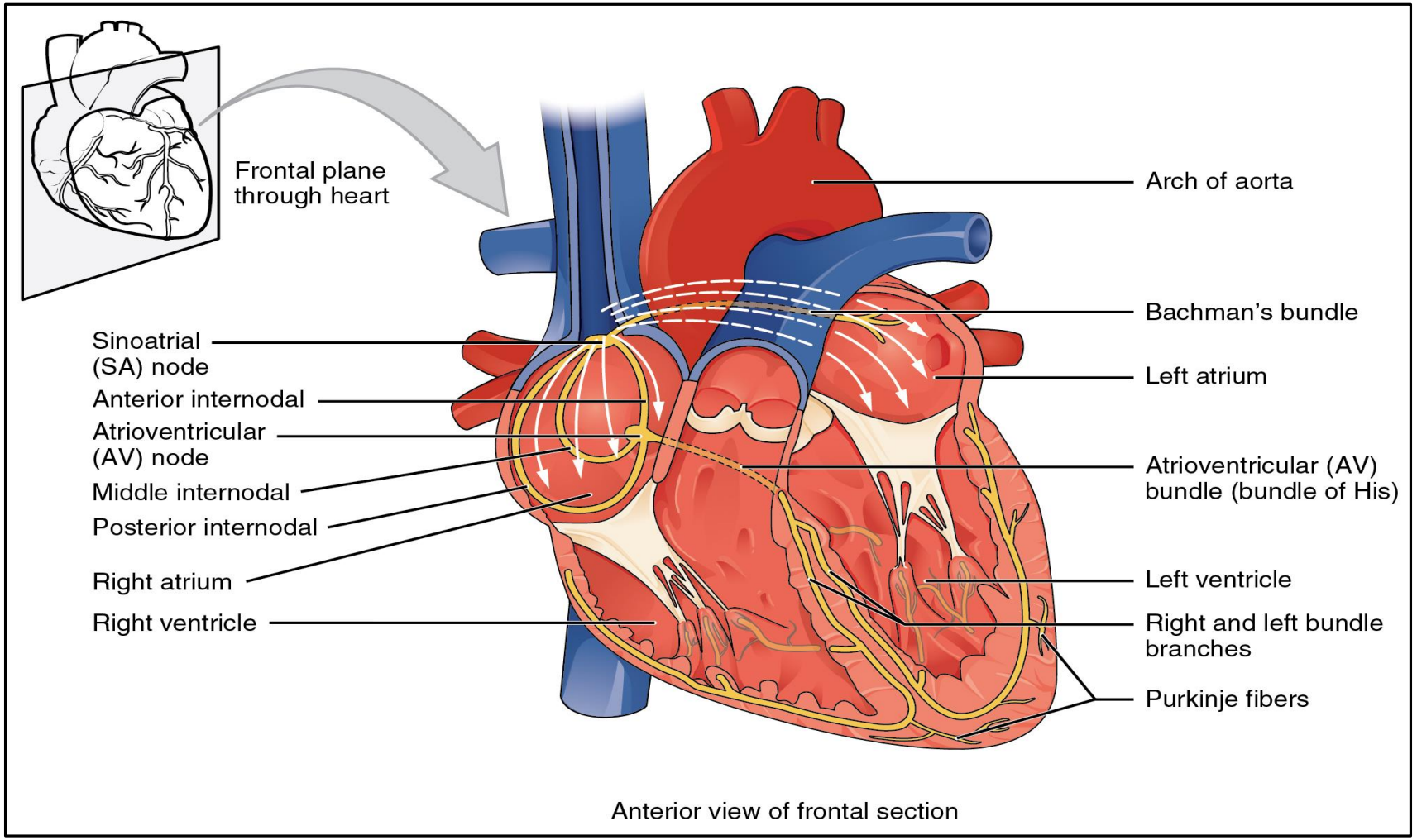


Figure: Download for free at http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@6.27.

Berne R, Levy M. Cardiovascular Physiology. 8th ed. : Mosby; 2001.

The Heart: Function

Pumping:

- Right side of the heart (RA and RV) pump blood to the lungs to be oxygenated
- Left side of the heart (LA and LV) oxygenated blood pumped out to the body supplying the fuel that cells need to function

- **Ejection fraction** determines how well your heart pumps with each beat
  - **Left ventricular ejection fraction (LVEF)** measurement of the percentage of blood is being pumped out of the left ventricle with each contraction. Commonly measured by Echocardiogram

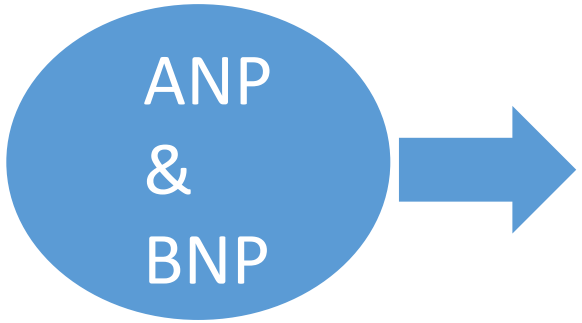
LVEF	
≥ 55 %	Normal
45-54%	Mildly abnormal
30-44 %	Moderately abnormal (may confirm diagnosis of heart failure)
<35%	Severely abnormal

Solomon S, Wu J, Gillam L, Bulwer B. Echocardiography In: Mann DL, Zipes D, Libby P, Bonow R, Braunwald E eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10 ed: Elsevier; 2015.

The Heart: Function

Endocrine - Cardiomyocytes synthesize and secrete

- Atrial natriuretic peptide (ANP) – atria
- B-type - brain natriuretic peptide (BNP) - ventricles
  - Most sensitive and specific indicator of ventricular dysfunction
  - Used in diagnoses and prognosis in CHF



Long-term regulation of sodium and water balance, blood volume and arterial pressure

BNP levels	Interpretation
< 100 pg/mL	**Normal (No heart failure)**
100-400 pg/mL	**Possible HF**
> 500 pg/mL	**Heart failure**

Kim H-N, Januzzi JL. Natriuretic Peptide Testing in Heart Failure. *Circulation.* 2011;123(18):2015-2019

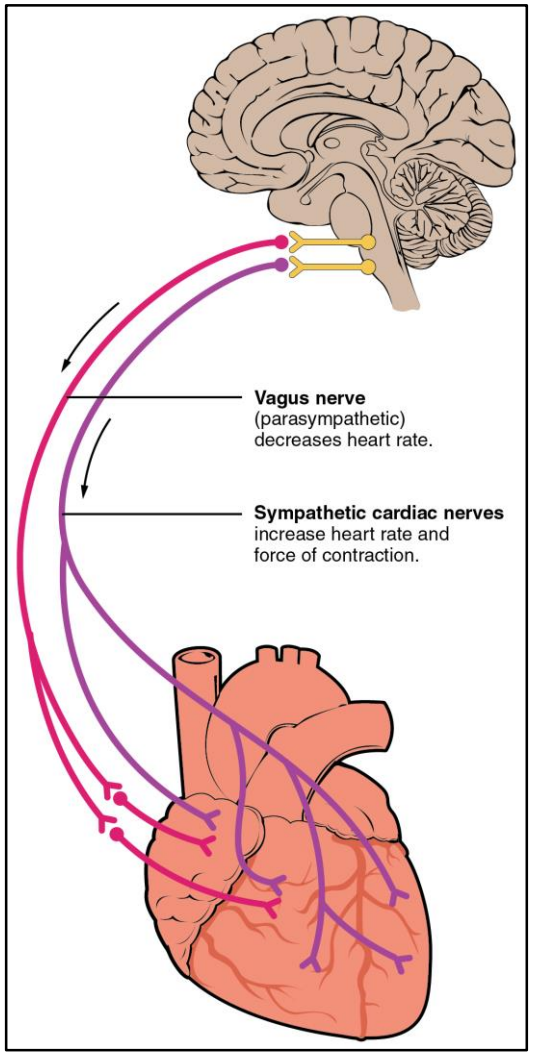
Cardiovascular Centers

HR control

- Cardiovascular centers in the medulla oblongata

Autonomic Innervation

- Sympathetic Pathways
- Parasympathetic Pathways



Berne R, Levy M. Cardiovascular Physiology. 8th ed. : Mosby; 2001.

Figure: download for free at http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@6.27.

The Cardiovascular System: Summary

Cardiovascular regulation

- Ensures adequate circulation to body tissues

Cardiovascular centers

- Control heart and peripheral blood vessels

Cardiovascular system responds to

- Changing activity patterns
- Circulatory emergencies

Berne R, Levy M. Cardiovascular Physiology. 8th ed. : Mosby; 2001.

Cardiovascular Responses to Normal Sleep

Autonomic responses during sleep

Sleep State-dependent changes in SNA and BP

NREM: Generalized cardiovascular deactivation and baroreflex resetting

- ↓Vagal activity → ↓HR
- ↓Sympathetic vasomotor tone (Muscle sympathetic nerve activity (MSNA)) → ↓BP

REM: BP and HR are similar to levels recorded during quiet wakefulness

- ↑Sympathetic vasomotor tone (MSNA)
- Transient baroreflex suppression
- Fluctuations in HR

Okada et al. Neurology 1991; 41(12):1961–1966.

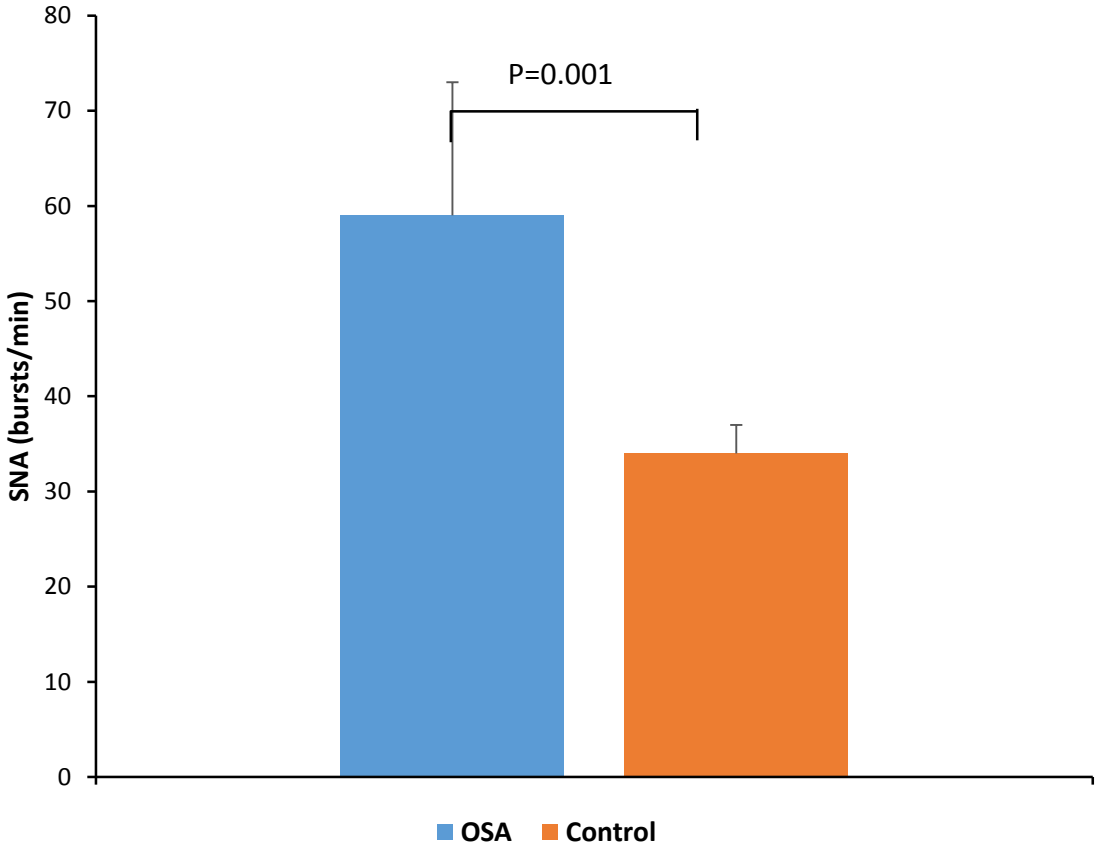
Cardiovascular Responses During Sleep in OSA patients

Blood Pressure and sympathetic activity during obstructive apnea events

Prospective study comparing OSA to non-OSA patients has shown:

Patients with OSA

- high levels of sympathetic nerve activity (SNA) even when awake
- Blood pressure and sympathetic nerve activity did not fall during any stage of sleep.



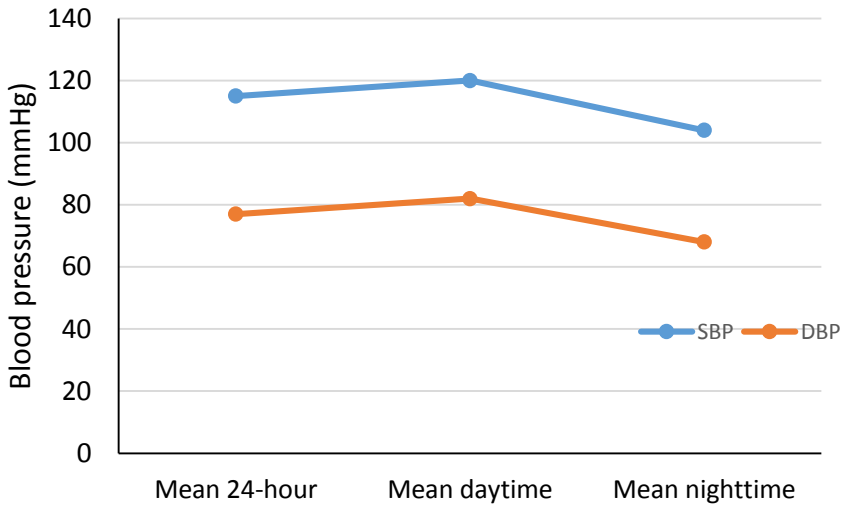
Somers VK et al, J Clin Invest 1995;96(4):1897-1904.

Nocturnal blood pressure profile

24 hr. ambulatory blood pressure monitoring

Normotensive Non-OSA patient

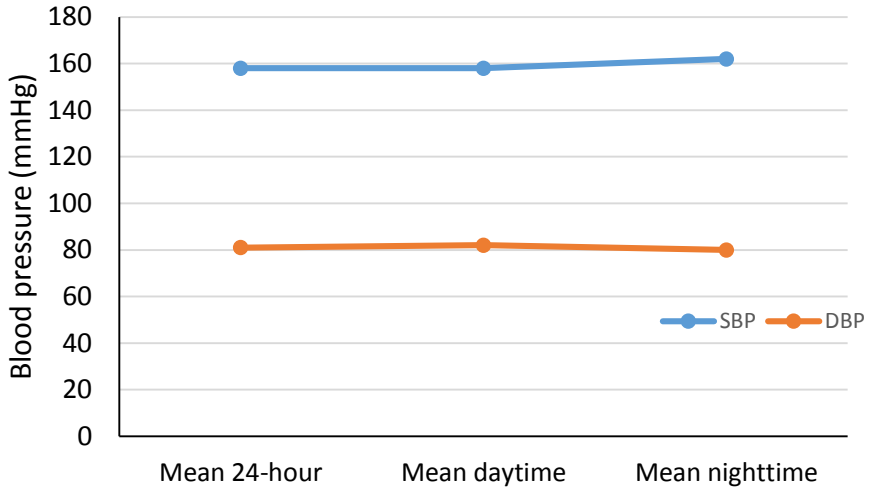
Dipping pattern of nocturnal BP (17% reduction in mean arterial pressure)



Gardner SF et al , J Am Board Fam Pract 2001;14:166 –71.)

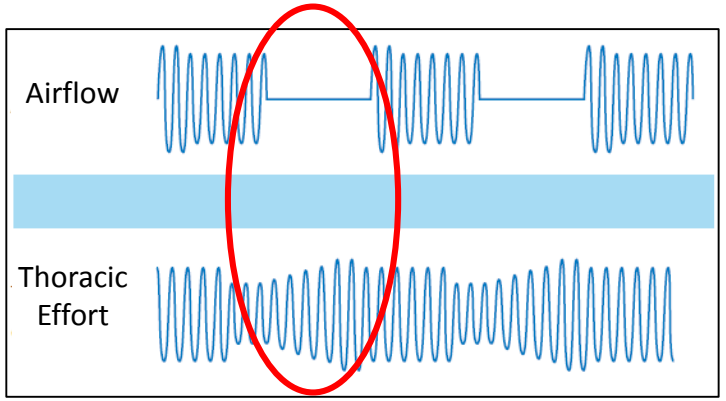
Newly diagnosed OSA

Non-dipping pattern of nocturnal BP possibly due to exaggerated sympathetic nervous system activity



Rimoldi SF et al, Eur. Heart J. 2014;35(19):1245-1254

Pathophysiologic events in OSA



↓ oxyhemoglobin saturation

Stimulation of peripheral chemoreceptors

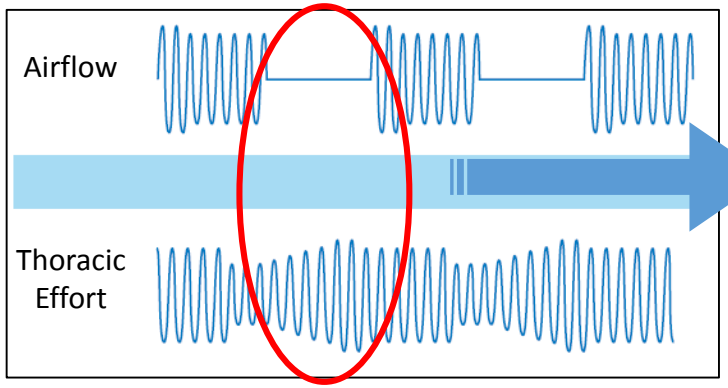
Central Nervous system stimulation

↑Sympathetic vasomotor tone

↑ Arterial blood pressure

Somers VK & Abboud FM Sleep 1993; 16(8 suppl):S30–S33; discussion S33–S34.

Effects of OSA on the Right and Left Ventricle



Effort to breath against an occluded upper airway

Exaggerated negative intrathoracic pressure

↑ venous return and right ventricular (RV) pre-load

↑ left ventricular (LV) transmural pressure ↑ LV afterload

OSA-induced hypoxia

PA vasoconstriction and pulmonary hypertension

RV distension and leftward displacement of the interventricular septum

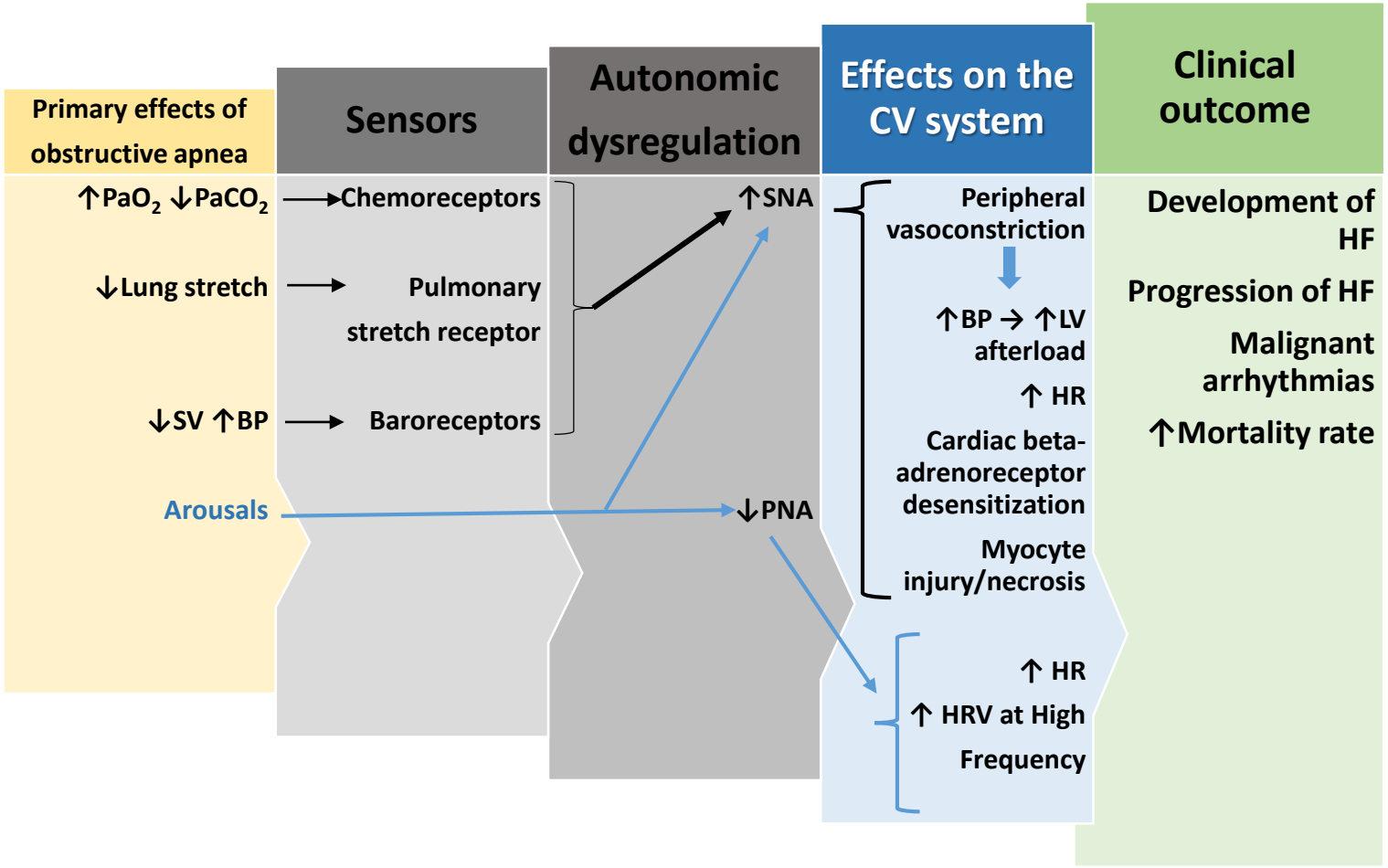
↑ myocardial O2 demand
↓ coronary blood

myocardial ischemia
↓ cardiac contractility
↓ diastolic relaxation

Over time, such stresses may contribute to development or progression of cardiac remodeling, hypertrophy, and failure

Kasai T & Bradley TD, J. *Am. Coll. Cardiol.* 2011;57(2):119-127.

Cardiovascular Autonomic Effects of OSA

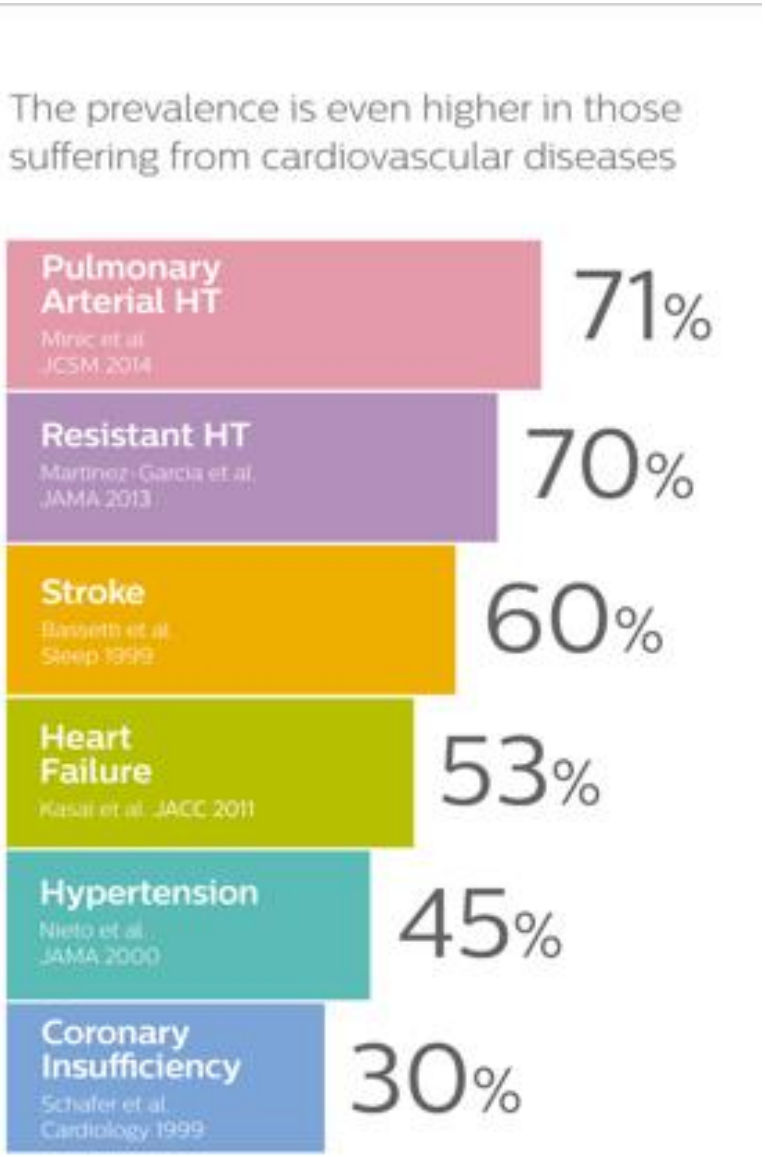


Kasai T & Bradley TD, J. *Am. Coll. Cardiol.* 2011;57(2):119-127.

Sleep Apnea and Cardiovascular Diseases

SA is strongly associated with a number of CVDs including :

- Hypertension
- Resistant HTN
- Transient ischemic attack
- Stroke
- Pulmonary hypertension
- Heart Failure
- Coronary Heart Disease
- Atrial Fibrillation
- Myocardial ischemia
- Myocardial infarction
- Sudden death

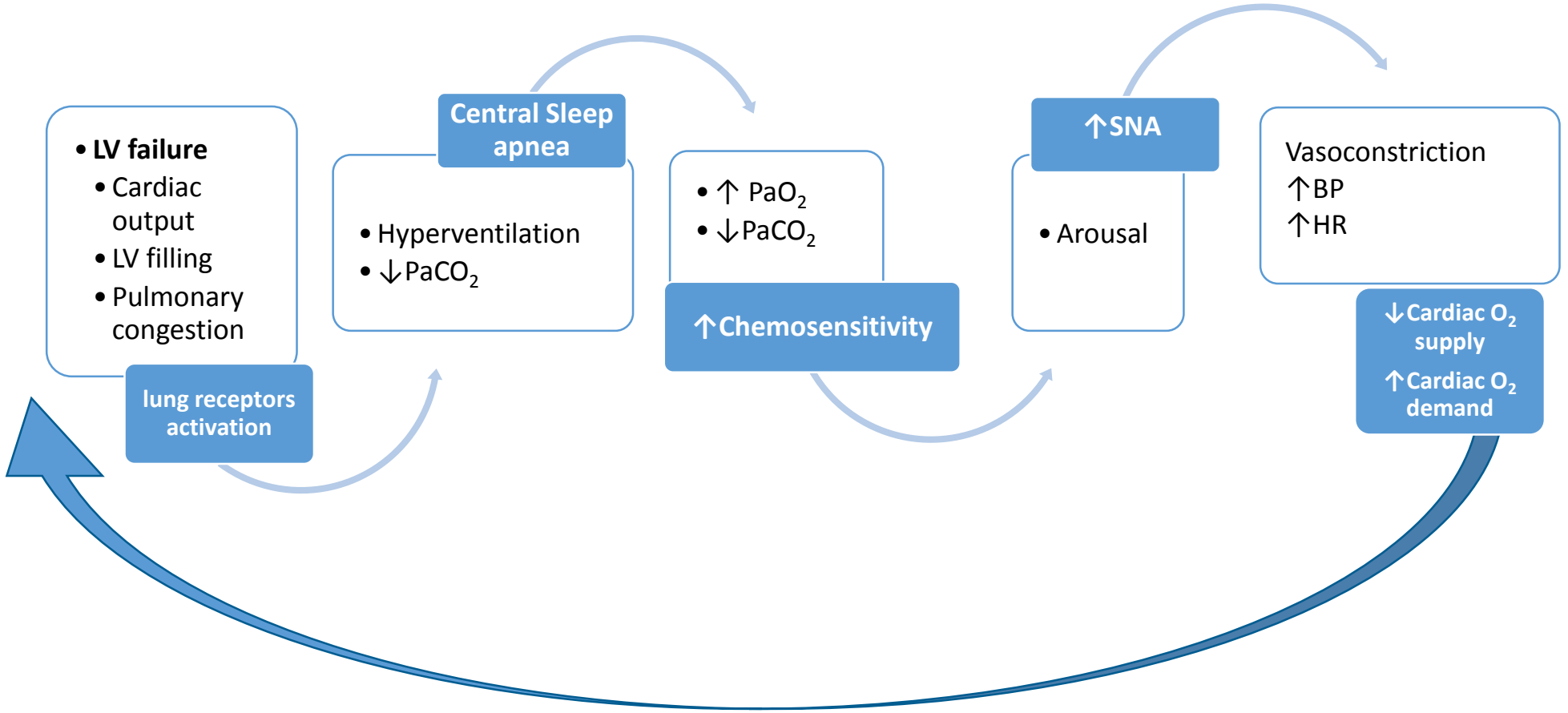


Heart Failure(HF)

- Presence of sleep-disordered breathing is recognized as one of the factors contributing to the excess morbidity and mortality in HF
- Central sleep apnea is highly prevalent in HF: 30% to 50% of patients
- Respiratory instability in HF lead to the rhythmic pattern of breathing referred to as Cheyne-Stokes Breathing (CSB)
- CSB - recurrent cycles of smooth and gradual crescendo–decrescendo changes in tidal volume with an intervening central apnea in a patient with HF
- CSB is unique to patients with HF as it has a long cycle time reflecting the prolonged circulation time- a pathological feature of heart failure with reduced ejection fraction

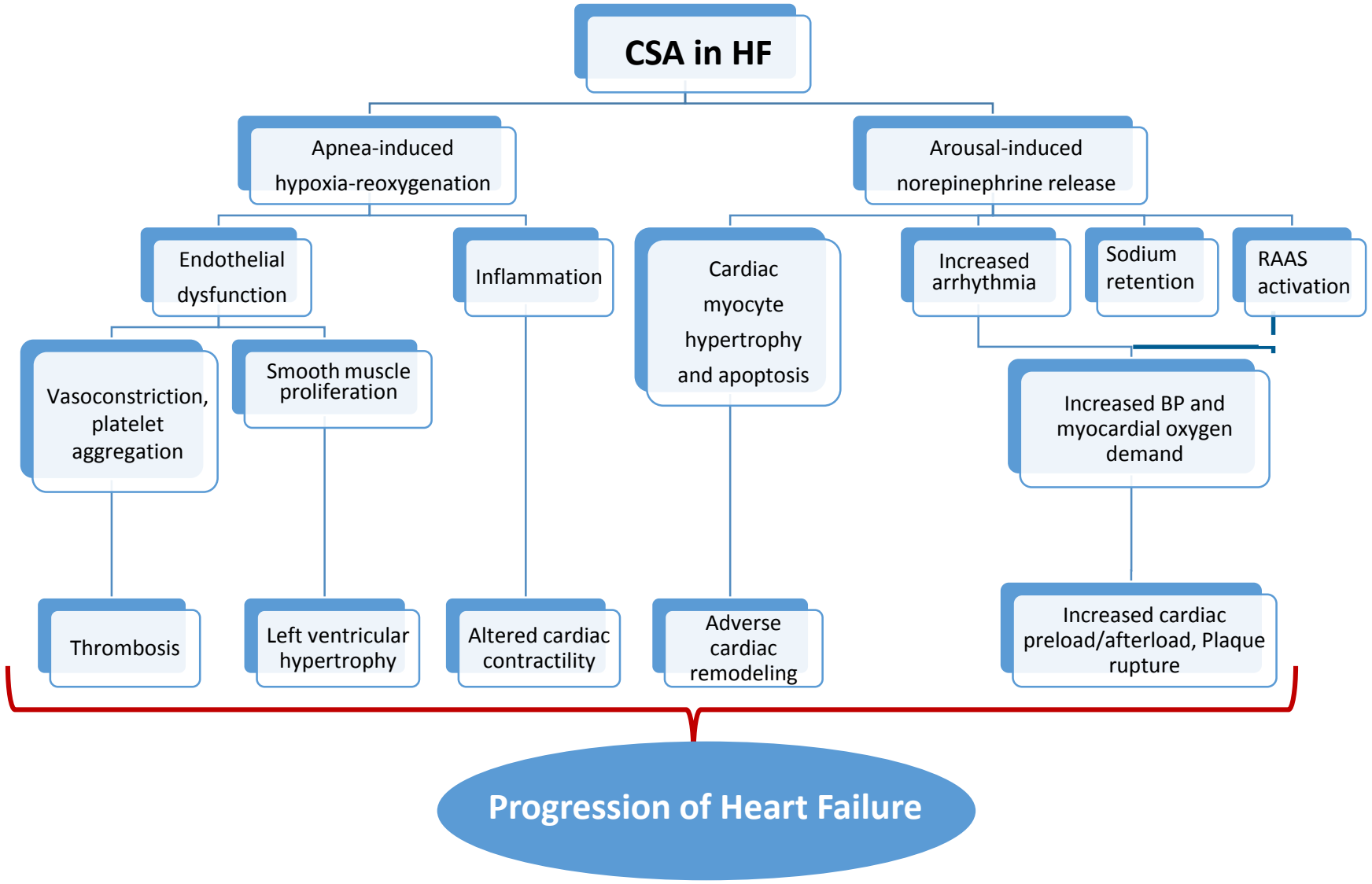
Javaheri,S. , et al .,Journal of the American College of Cardiology Feb 2017, 69 (7) 841-858

Mechanisms leading to periodic breathing in HF



Yumino & Bradley. Proc Am Thorac Soc 2008 5: 226-236
Bradley D & Floras JS Circulation. 2003;107:1822-1826

Pathophysiologic Consequences of CSA in HF



Constanzo MR et al. J Am Coll Cardiol 2015; 65: 72-84

Servo ventilation: CSA in HF

SERVE-HF trial

International, multicenter (91), randomized, parallel-group, event-driven study

- N= 1325 patients, follow-up 2 years.
- Symptomatic chronic systolic HF (LVEF ≤45%)
- AHI ≥15 events/h**,** predominantly CSA
- Intervention: Optimal cardiac therapy with or without ASV
- Primary combined end-point: Time to first event of
  - Death from any cause, life-saving cardiovascular intervention*, or unplanned hospitalization for worsening heart failure

Results

- No difference in primary endpoint.
- All-cause mortality and cardiovascular mortality significantly higher under ASV

Cowie et al. NEJM 2015; 373(12):1095-105

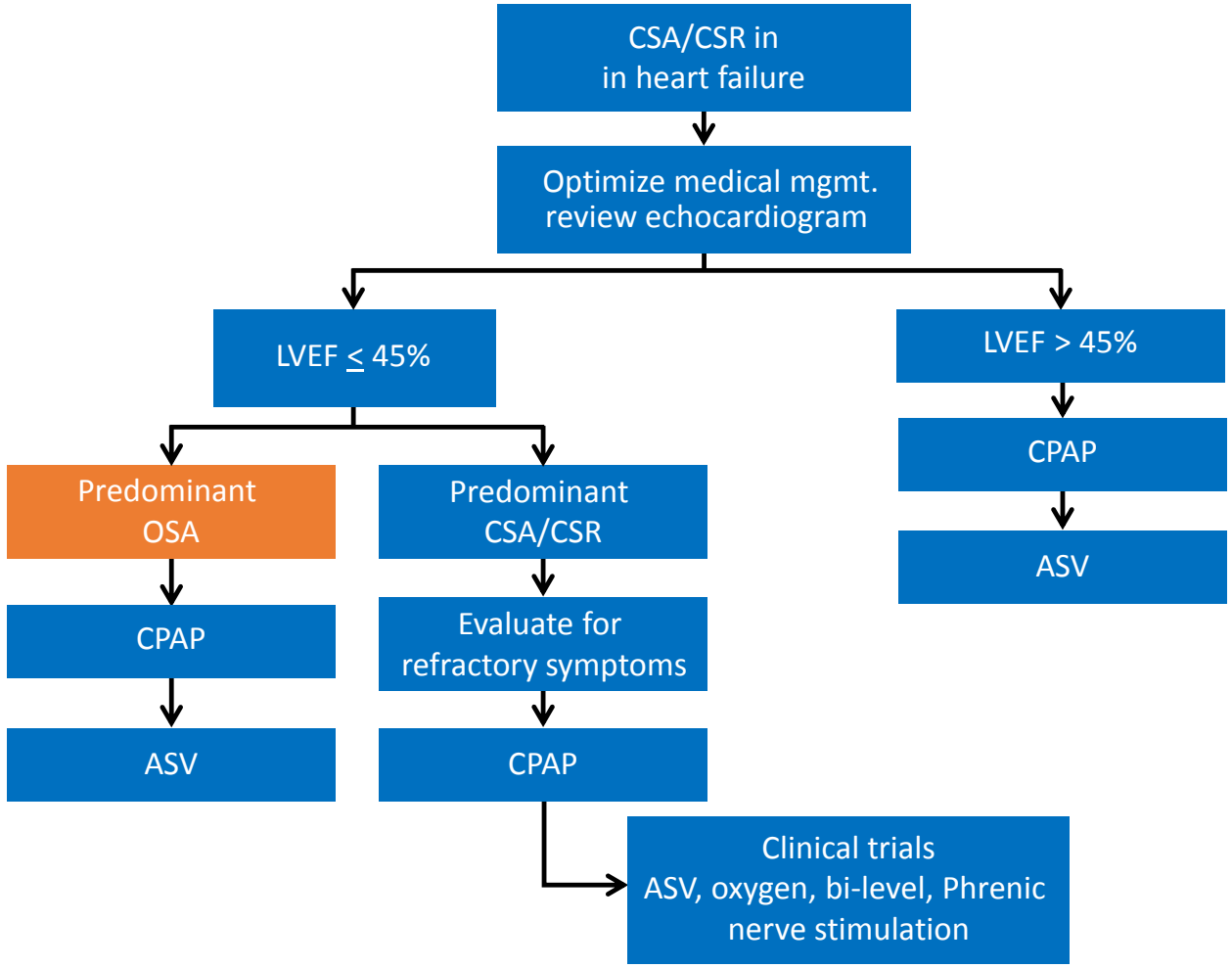
SERVE-HF trial - Summary

- Bias due to unblinded study design
- The study was conducted in patients who had heart failure with reduced ejection fraction, and therefore the results can NOT be generalized to patients who have heart failure with preserved ejection fraction
- The study results also can NOT be extrapolated to patients with predominantly obstructive sleep apnea
- Addition of adaptive servo-ventilation to guideline based medical treatment did not improve the outcome **in patients with HFrEF and CSA** despite effective control of CSA

Cowie et al. NEJM 2015; 373(12):1095-105

CSA/CSR in Heart Failure

Suggested PAP Therapy Protocol



Developed by Prof. Dr. Winfried Randerath

Ayas NT et al. AJRCCM 2015 192(2): 132-133 AASM (2015). "Special Safety Notice: ASV therapy for central sleep apnea patients with heart failure."
http://www.aasmnet.org/articles.aspx?id=5562.

Hypertension (HTN)

- Causal link between OSA and systemic hypertension has been established
- Several studies have shown that sleep apnea increases the relative risk for hypertension, independent of other confounding factors
- **Treatment**: CPAP therapy and lifestyle modification
- Studies using 24-h BP monitoring consistently report drops of 2 to 2.5 mm Hg and 1.5 to 2 mm Hg in systolic blood pressure and diastolic blood pressure, respectively, compared with subtherapeutic or conservative treatment, with greater reductions in patients with resistant HTN (between 4.7 to 7.2 mm Hg and 2.9 to 4.9 mm Hg for SBP and DBP, respectively)
- CPAP has also been demonstrated to reverse nondipper or riser nocturnal BP patterns in OSA patients

Javaheri,S. , et al .,Journal of the American College of Cardiology Feb 2017, 69 (7) 841-858

Pulmonary Hypertension (PHTN)

- About 10% of patients with OSA have PHTN (defined as the mean pulmonary artery pressure ≥25 mm Hg)
- **Treatment:** Multiple observational studies demonstrate that treating OSA with CPAP improves PHTN
- In the only small randomized crossover study (therapeutic vs. sham CPAP), 12 weeks of treatment resulted in a significant decrease in pulmonary artery systolic pressure (from a mean of 30 to 24 mm Hg)
- The reduction was greatest (8.5 mm Hg) in patients with baseline PHTN (pulmonary artery systolic pressure ≥30 mm Hg by echocardiography)
- The American College of Cardiology/American Heart Association expert consensus document recommends polysomnography to rule out OSA for all patients with PHTN

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TIA/Stroke

- Sleep apnea is highly prevalent in patients with stroke or TIA
- OSA also is associated with increased risk for incident stroke
- **Treatment :** CPAP therapy
- There is some evidence that early CPAP therapy has positive effects on long-term survival in ischemic stroke patients with moderate-to-severe OSA
- The American Heart Association/American Stroke Association guideline states: “A sleep study might be considered for patients with an ischemic stroke or TIA on the basis of the very high prevalence of sleep apnea in this population and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general population”

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Arrhythmias

- Cardiac arrhythmias are common problems in OSA patients
- Individuals with severe SDB are two- to four-times more likely to develop complex arrhythmias than those without SDB
- 49% of patients with atrial fibrillation have OSA compared with 32% in general cardiology practice
- **Treatment** : CPAP treatment is associated with a significantly decreased recurrence rate of AF, even after electrical cardioversion or ablative therapies
- Patients are less likely to progress to more permanent forms of AF and have significantly reduced occurrence of paroxysmal AF compared with untreated patients

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Summary

- Adequately treated OSA has been associated with improved cardiovascular outcomes
- Patients with untreated OSA were 2.68 times more likely to suffer a non-fatal CV event compared to those whose OSA was effectively treated with CPAP
- Patients with untreated OSA were 2.5 times more likely to suffer a fatal CV event compared to those whose OSA was effectively treated with CPAP

Marin, J.M,. et al .,Lancet. 2005 Mar 19-25;365(9464):1046-53

References

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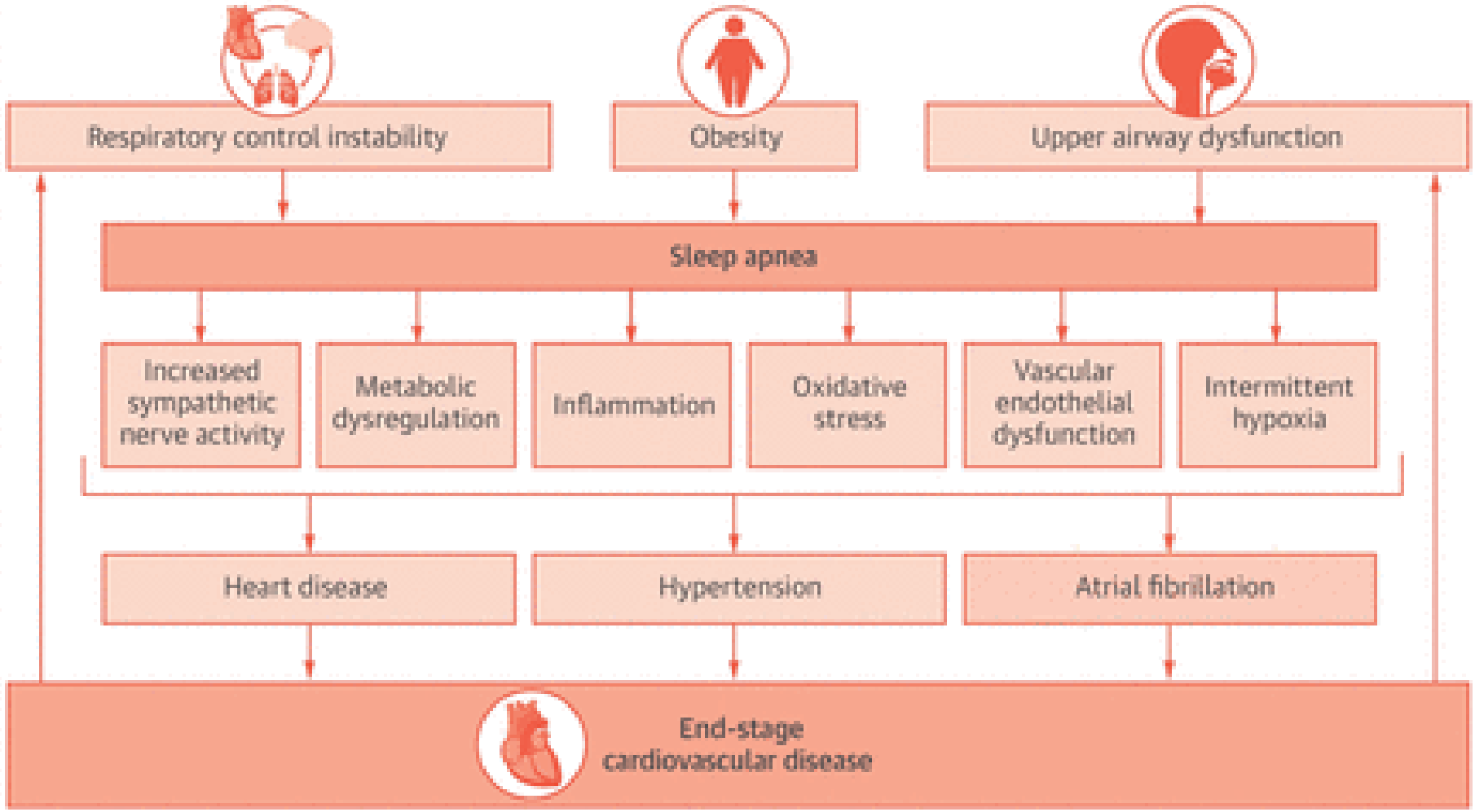
Questions???

CENTRAL ILLUSTRATION: Potential Etiological Risk Factors for Sleep Apnea and the Downstream Consequences



Javaheri, S. et al. J Am Coll Cardiol. 2017;69(7):841-58.

SERVE-HF vs ADVENT-HF trial

	SERVE- HF	ADVENT HF
Type of SDB	Predominantly CSA	Non sleepy OSA (64%)
Device algorithm	Did not allow lower end-exp pressure and min PS (5-3 cmH2O)	Lower default end-exp pressure and min PS (4 - 0 cmH2O)
ASV titration	**Not centrally reviewed**	Reviewed centrally *
ASV adherence	3.4 h/night	> 1 hour higher*
Nasal mask	15%	78%
Follow up	yearly	2x year
DSMB	**Reviewed data 2x in 7 years**	Every 6 months

*Device pressure setting prescribed by the core sleep laboratory to maintain the lowest pressures possible

Bradley & Floras Can Resp J 2015 2015 Nov-Dec;22(6):313