Sleep Apnea as a Cardiovascular Disease

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Ohio State University

Presentation Outline

- Case presentation
- Mechanism of the cardiovascular consequences of OSA
- OSA and heart failure
- SDB and heart failure: rationale for case finding

Case history

- 57 y/o school bus driver presents to the Sleep Center with:
  - Excessive daytime sleepiness
  - Snoring
  - Witnessed apnea
  - Spouse moved out of bedroom
- “ Not as focused as he used to be on the job”!

Sleep History

- Seven hours of allowed sleep per night- very tired in the morning
- Awakens 3-4 times at night to use rest room
- Persistent loud snoring
- Leg jerks and kicks, restless sleep

Case History

- **MHX:**
- **Hypertension**
- **Hypercholesterolemia**
- **ROS:**
- **35 lbs weight gain/past two year**
- **SoHx:**
- **40 Pack/year**

Physical Examination

- BMI 36
- Mallampati class III, lateral peri-tonsillar narrowing
- Neck collar size 18 inch
- Lungs clear
- Regular rhythm- no gallop
- No edema

- *OSA- why should I care?*
- *If I have to care, what should I do about it?*
- *Treatment of OSA in patients with heart disease is a waste of time !*

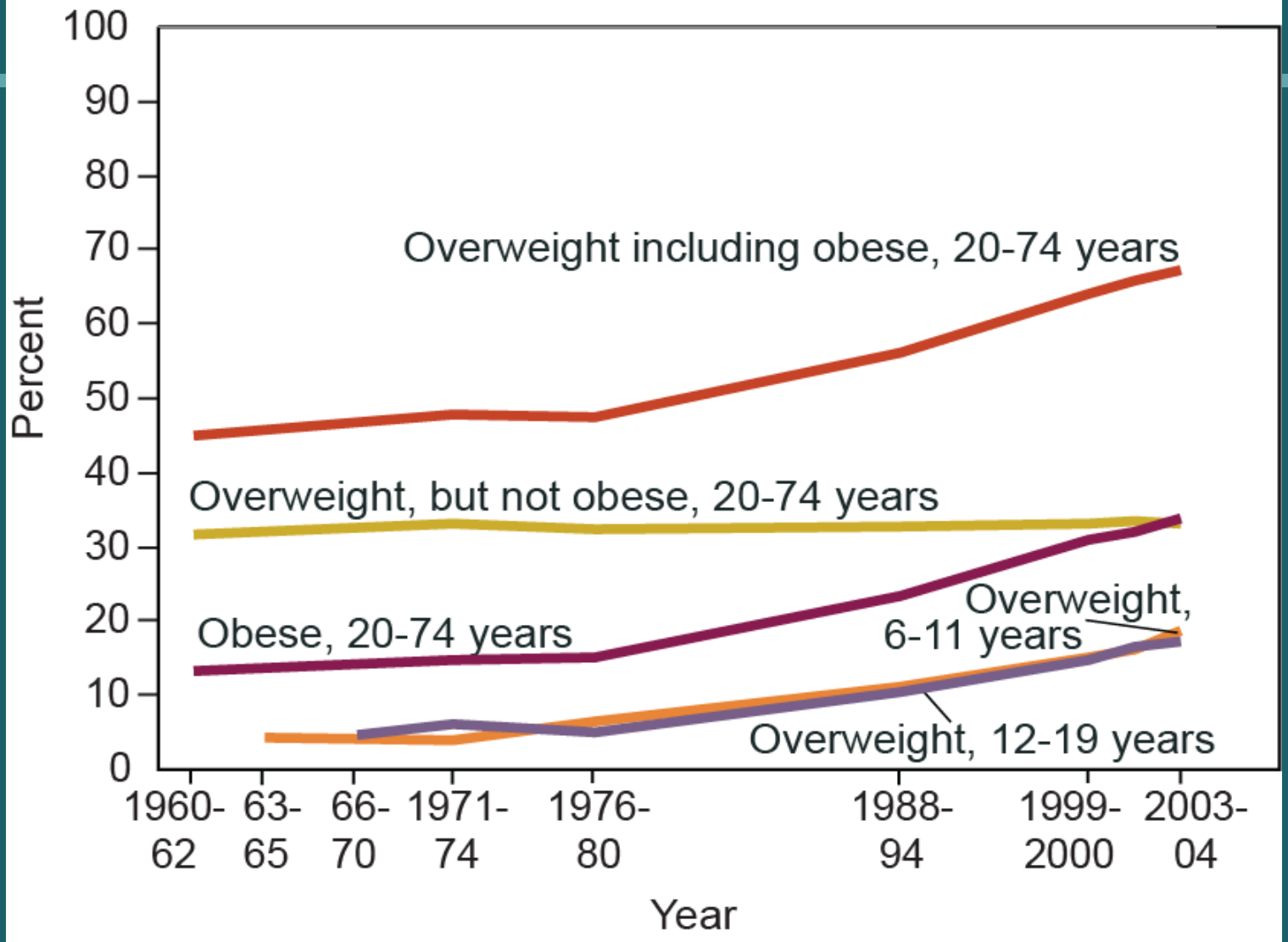
Prevalence of Obstructive Sleep Apnea

AGE (YR)	WOMEN			MEN		
	APNEA–HYPOPNEA SCORE			APNEA–HYPOPNEA SCORE		
	≥5	≥10	≥15	≥5	≥10	≥15
	percent of subjects (95% confidence interval)					
30–39	6.5 (1.4–11)	4.9 (0.6–9.8)	4.4 (1.1–7.3)	17 (9.6–25)	12 (5.4–19)	6.2 (1.9–10)
40–49	8.7 (4.2–13)	4.9 (1.7–8.1)	3.7 (1.0–6.5)	25 (18–32)	18 (11–24)	11 (6.7–16)
50–60	16 (5.2–26)	5.9 (0.0–12)	4.0 (0.0–10)	31 (21–40)	14 (7.5–20)	9.1 (5.1–13)
30–60*	9.0 (5.6–12)	5.0 (2.4–7.8)	4.0 (1.5–6.6)	24 (19–28)	15 (12–19)	9.1 (6.4–11)

*Values are adjusted to the age distribution of the survey population.

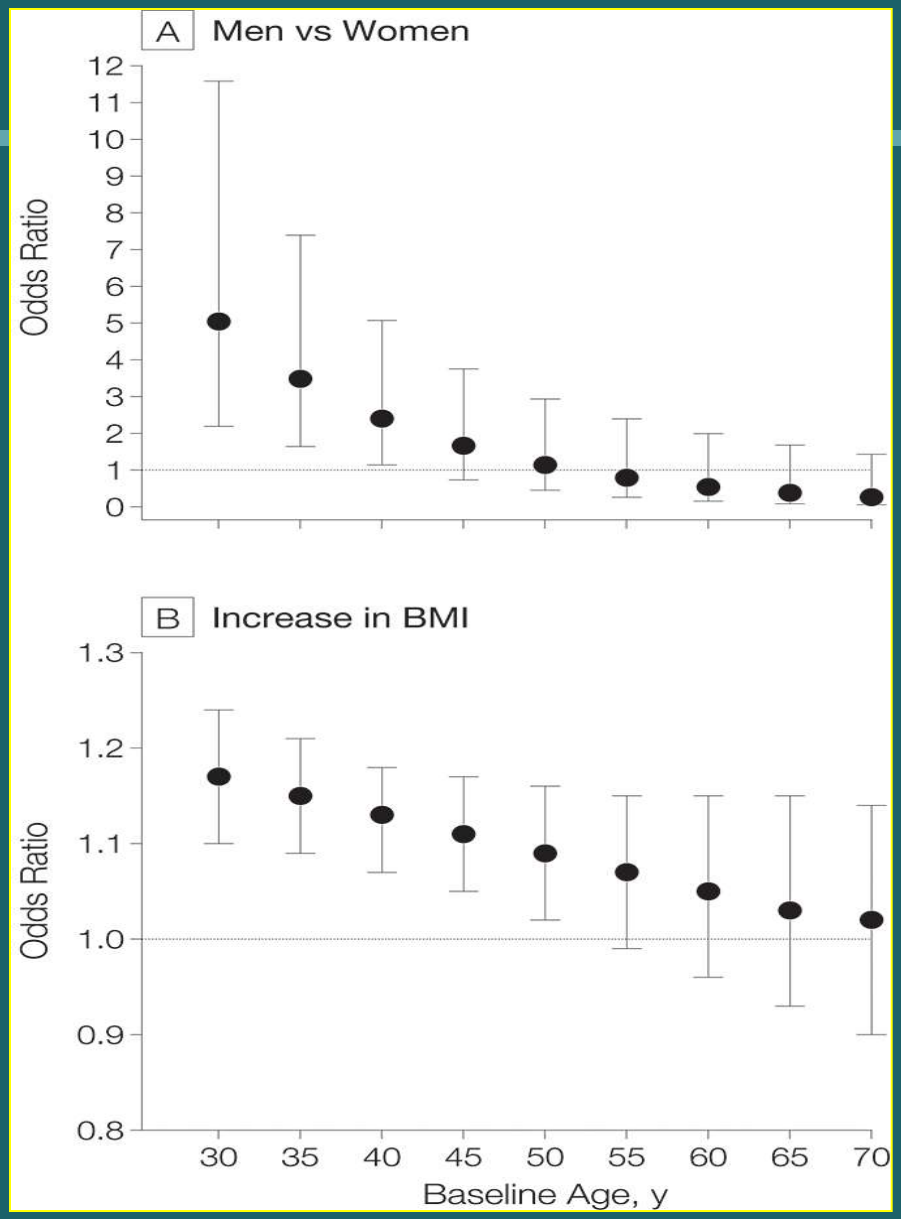
The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults
The Wisconsin Sleep Cohort, NEJM 1993

Overweight and obesity



SOURCES: Centers for Disease Control and Prevention, National Center for Health Statistics, *Health, United States, 2006*, Figure 13. Data from the National Health and Nutrition Examination Survey.

Gender, aging, and obesity



- The effects of gender and BMI change with aging.
- After the age of 50, *gender* becomes an unimportant variable.
- After the age of 60, *BMI* becomes an unimportant variable.

(Tishler PV, JAMA 2003)

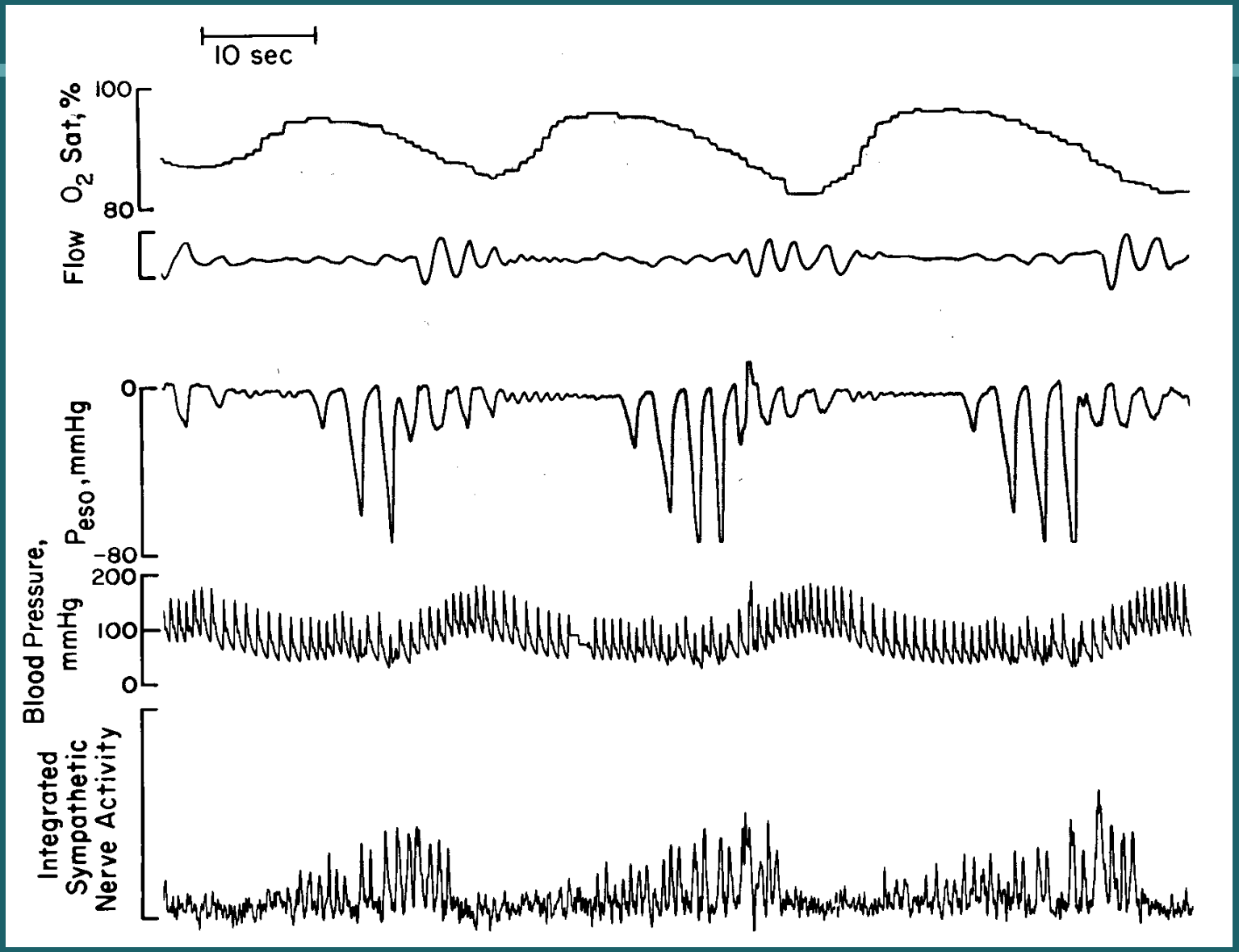
Symptoms of OSA

- Snoring
- Excessive daytime sleepiness
- Witnessed apneas
- Poor memory and concentration, irritability or personality changes
- Other: Dry throat, morning headache, and nocturia

Sleep Apnea- Presentation in a Cardiology Practice

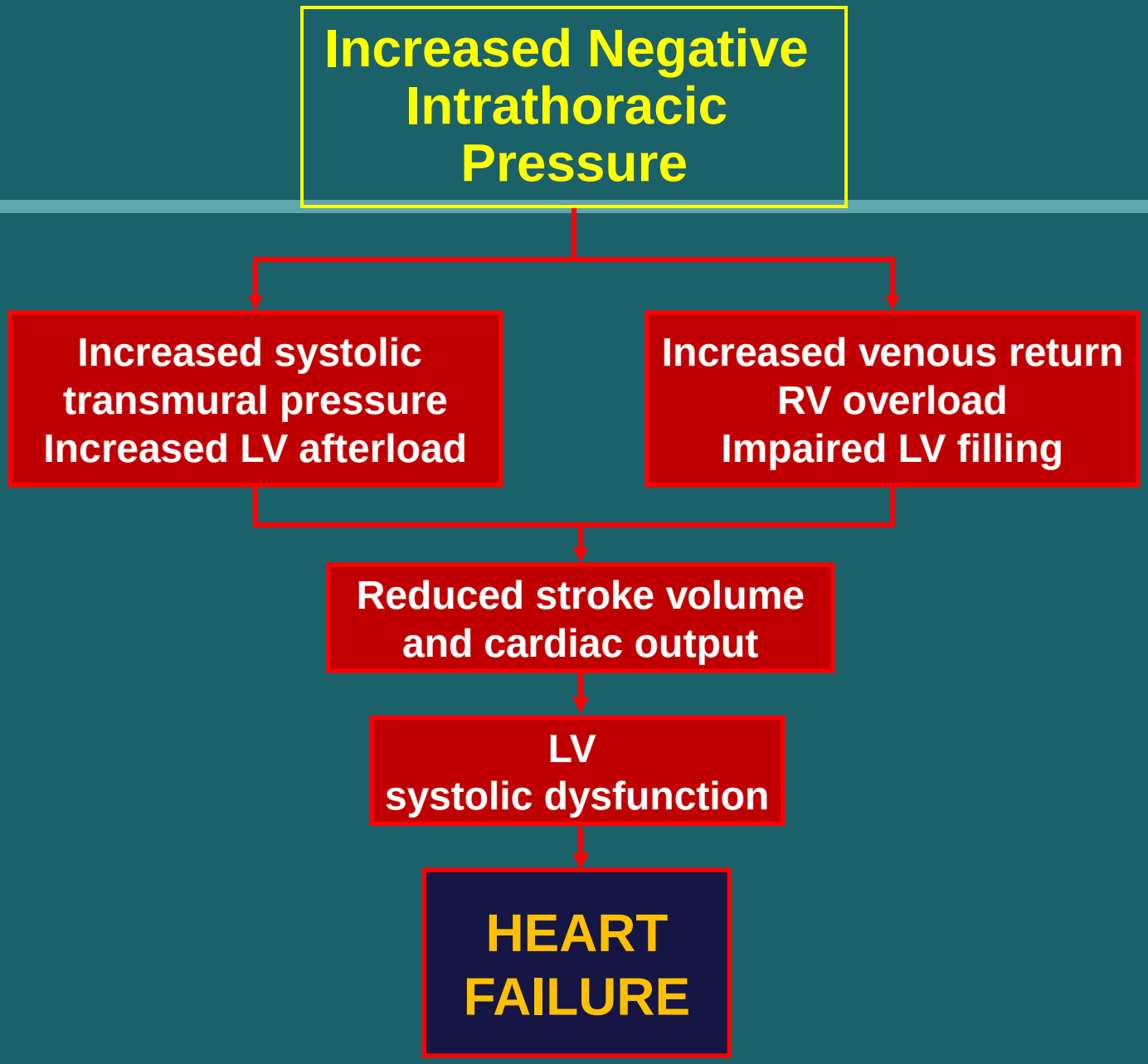
- Hypertension
- Left ventricular hypertrophy
- Nocturnal angina
- Myocardial infarction
- Bradyarrhythmias, ventricular arrhythmias
- Cor pulmonale
- Decompensated heart failure

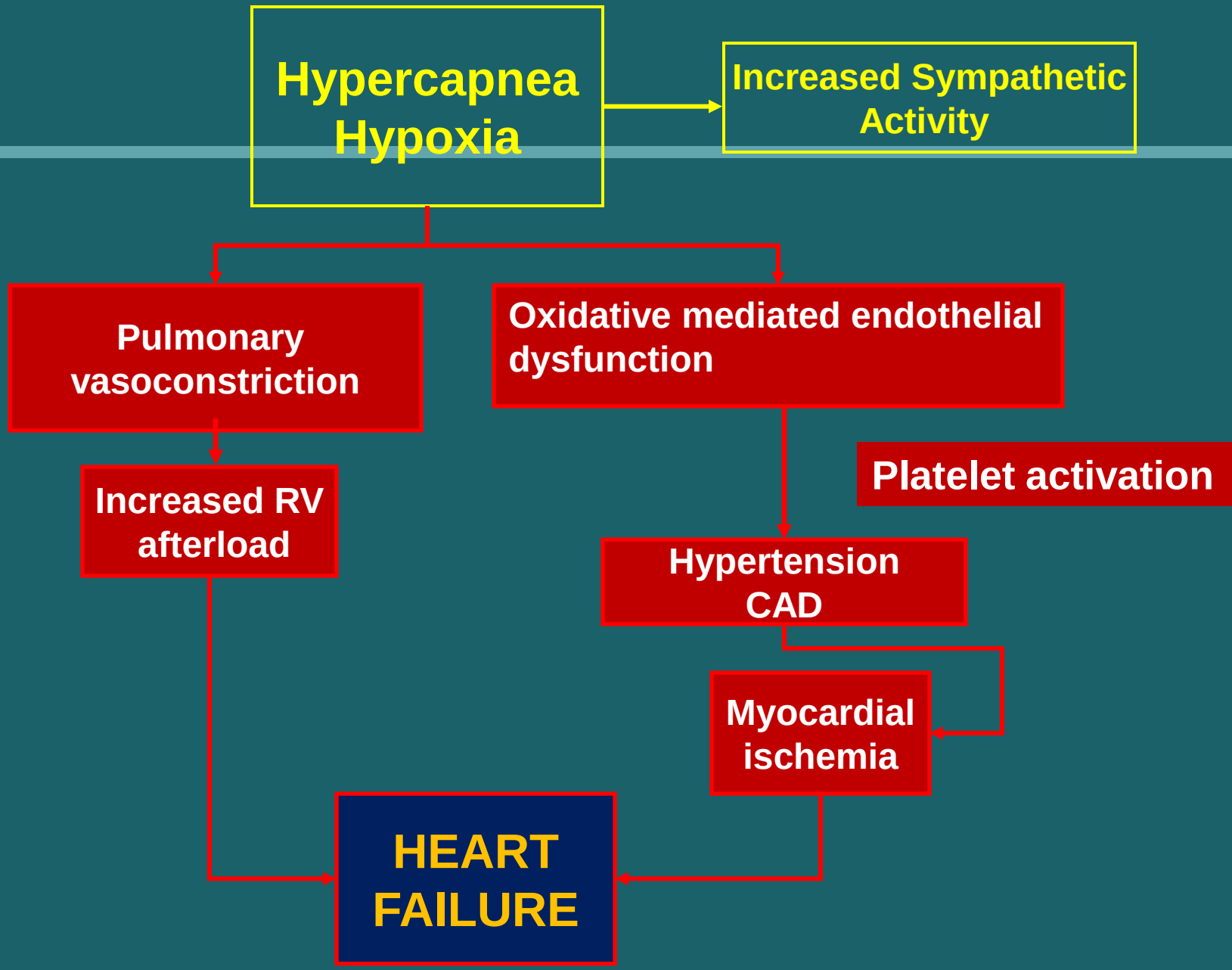
Cardiovascular Consequences of Sleep Apnea

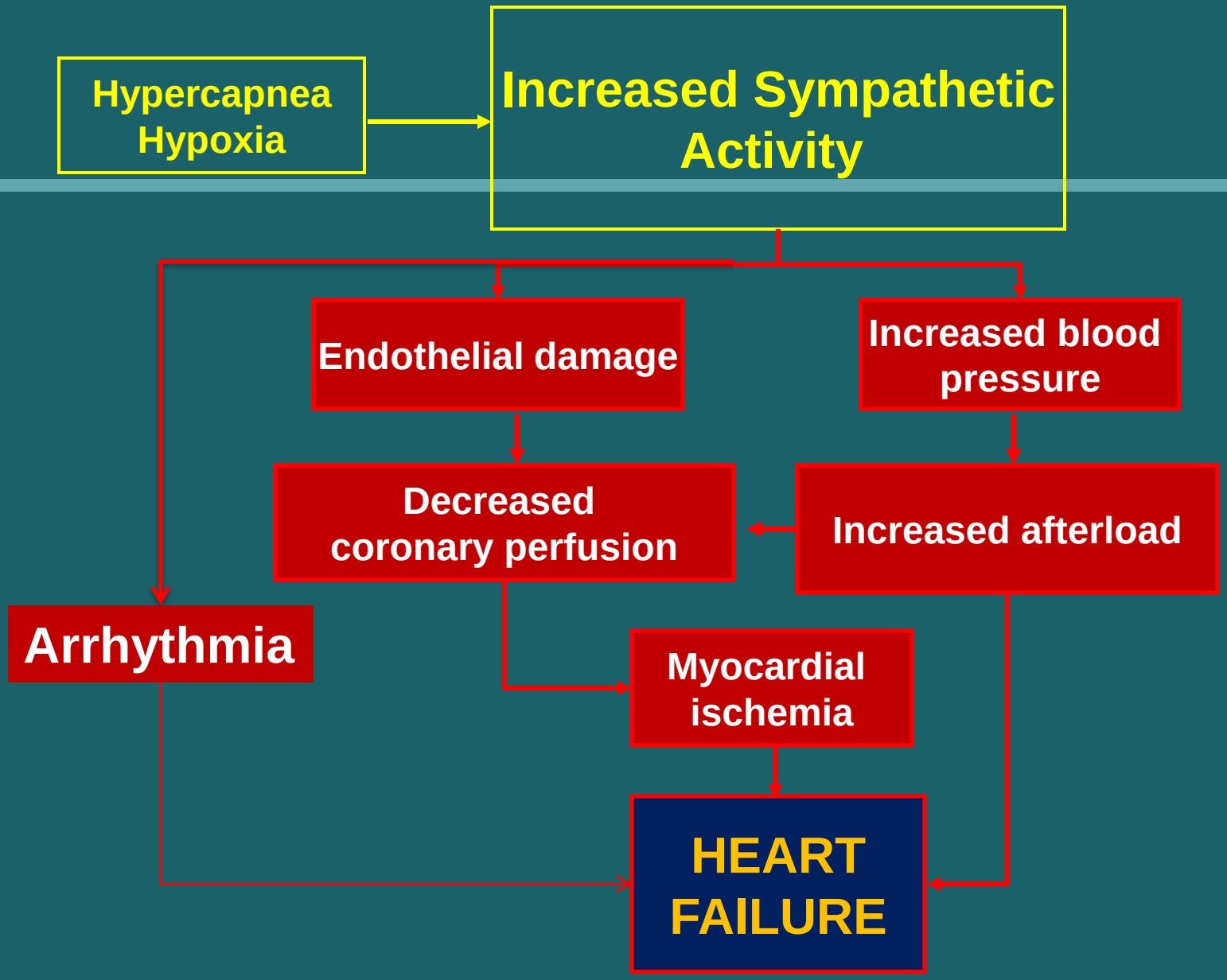


Components of the Cardiovascular response to Apnea

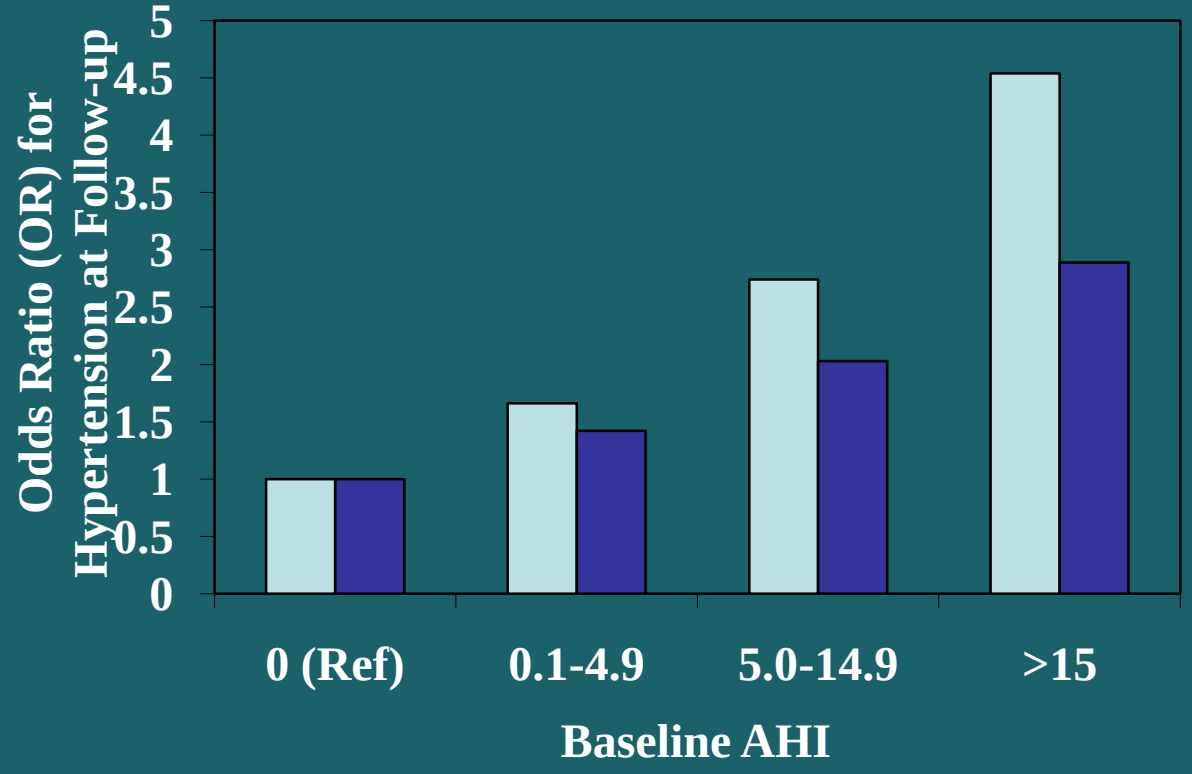
- Asphyxia (hypoxia-Hypercapnea)
- Increased sympathetic activity
- Blood pressure surge
- Arousal
- Respiratory Effort


Increased Negative Intrathoracic Pressure
Increased systolic transmural pressure
Increased LV afterload
Increased venous return
RV overload
Impaired LV filling
Reduced stroke volume and cardiac output
LV systolic dysfunction
HEART FAILURE


Hypercapnea
Hypoxia
Increased Sympathetic Activity
Pulmonary vasoconstriction
Oxidative mediated endothelial dysfunction
Increased RV afterload
Platelet activation
Hypertension
CAD
Myocardial ischemia
HEART FAILURE


Hypercapnea
Hypoxia
Increased Sympathetic Activity
Endothelial damage
Increased blood pressure
Decreased coronary perfusion
Increased afterload
Arrhythmia
Myocardial ischemia
HEART FAILURE

Association Between Sleep Apnea and Incident Hypertension During 4 Year Follow Up Period



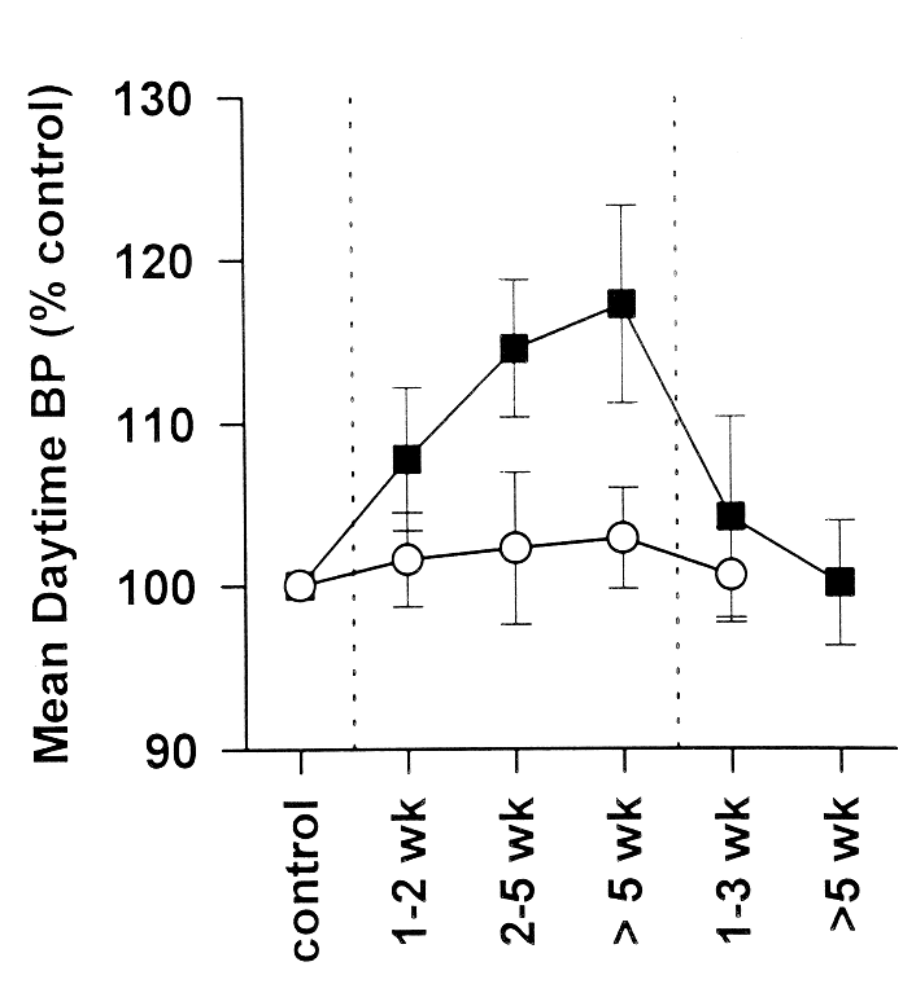
OR adjusted for baseline hypertension status

OR for above + age, gender, BMI, etc.

Hypertension = BP of at least 140/90 or use of anti-hypertensive medications

Peppard et al, NEJM 342:1378-1384, 2000

OSA- Induced Hypertension- Animal Model



Brooks, et al. J Clin Invest 99:106, 1997

Effect of CPAP on Blood Pressure in Hypertensive Patients

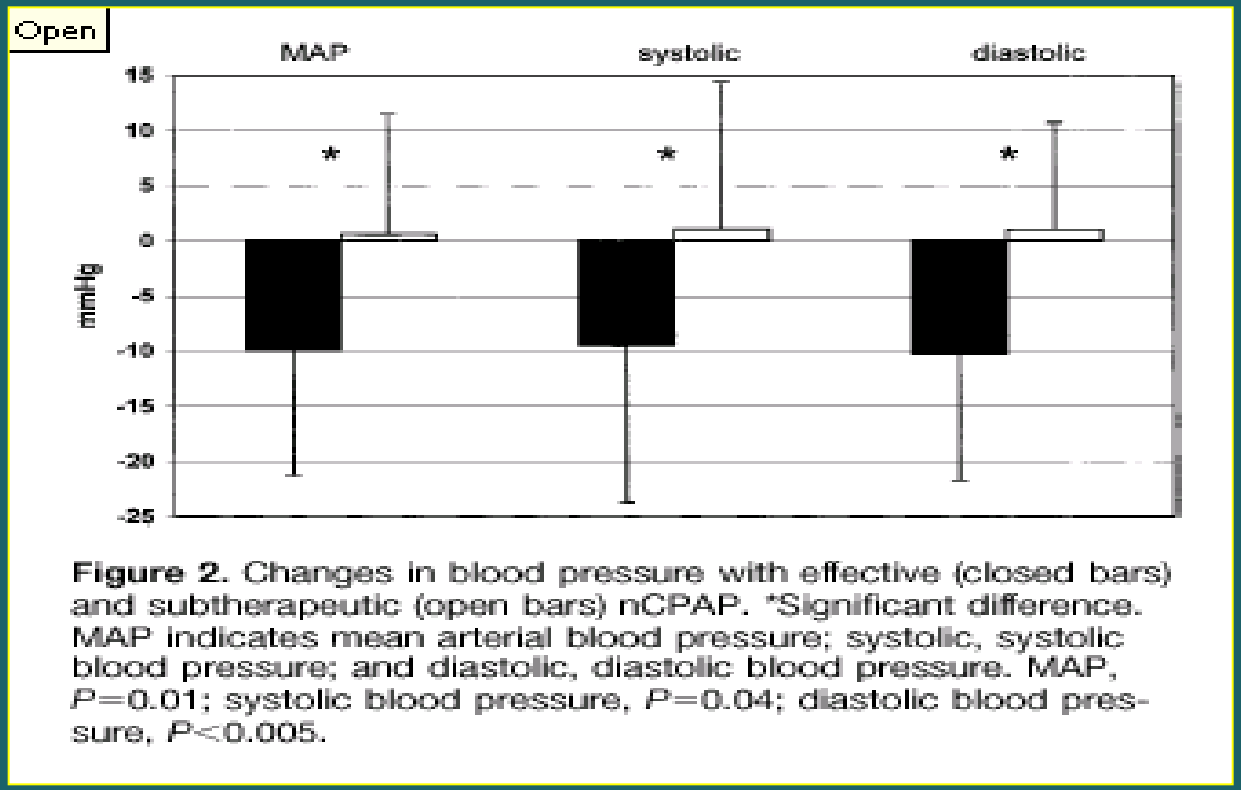


Figure 2. Changes in blood pressure with effective (closed bars) and subtherapeutic (open bars) nCPAP. *Significant difference. MAP indicates mean arterial blood pressure; systolic, systolic blood pressure; and diastolic, diastolic blood pressure. MAP, $P=0.01$; systolic blood pressure, $P=0.04$; diastolic blood pressure, $P<0.005$.

■ Therapeutic

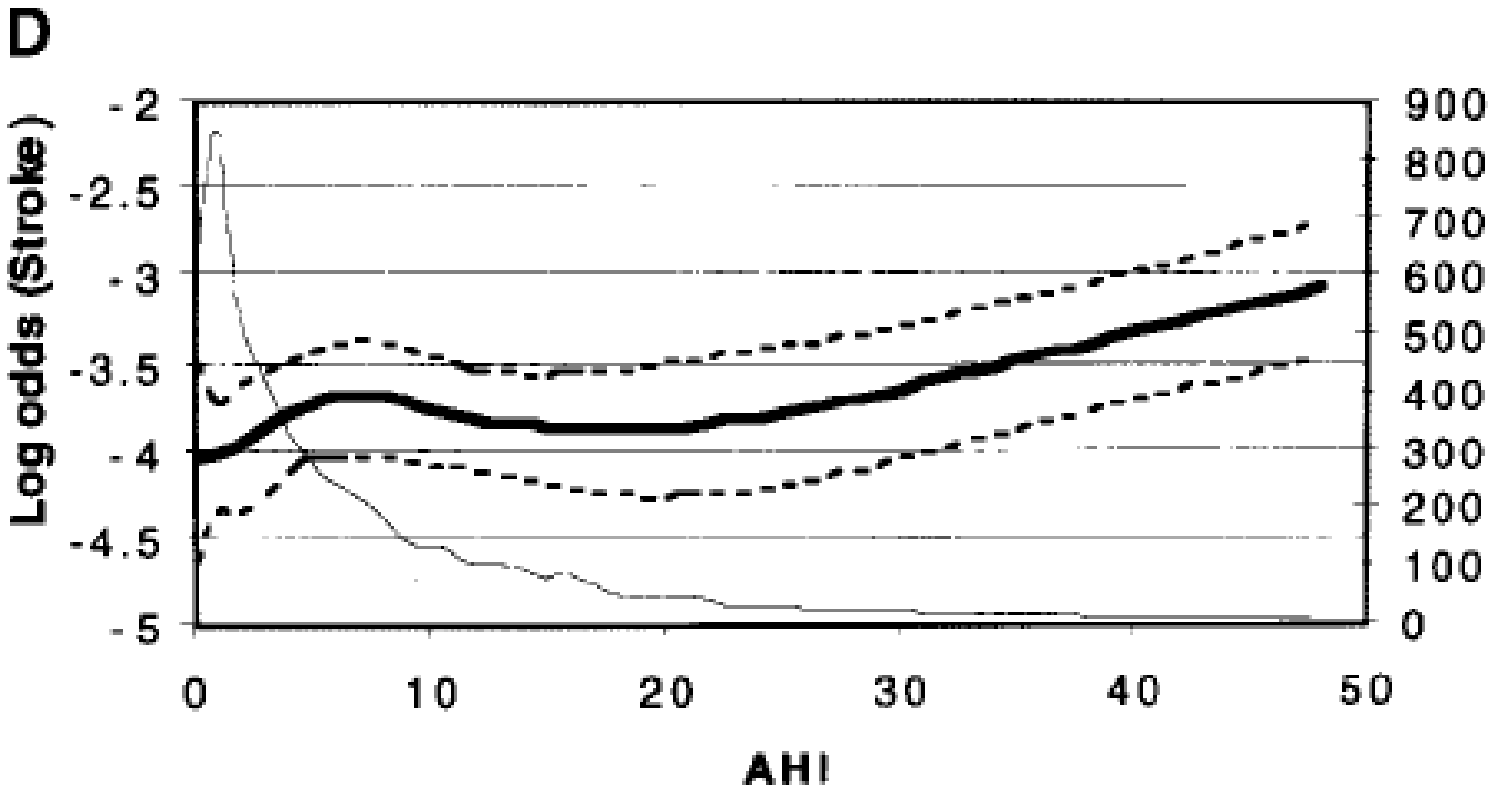
□ Subtherapeutic

Becker HF, Circ, 2003

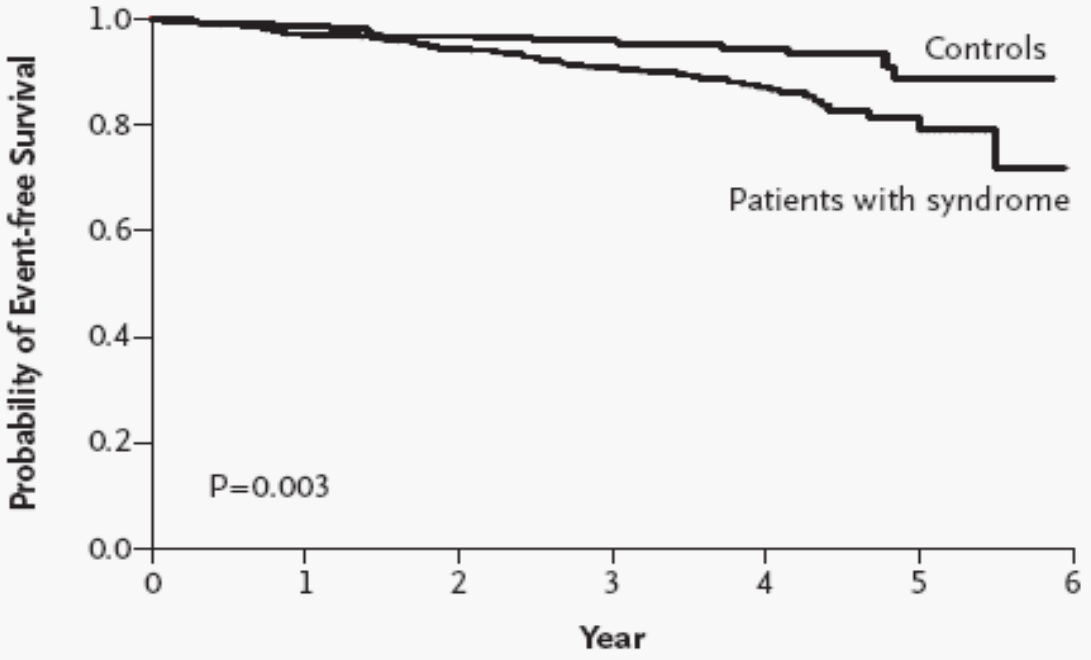
Hypertension and OSA

- OSA is a cause of hypertension
- Intermittent Hypoxia is the critical stimulus for the hypertensive response in patients with OSA.
- Treatment of OSA improves control of HTN

Stroke vs. AHI (Sleep Heart Health Study)



OSA and Risk of Stroke Recurrence

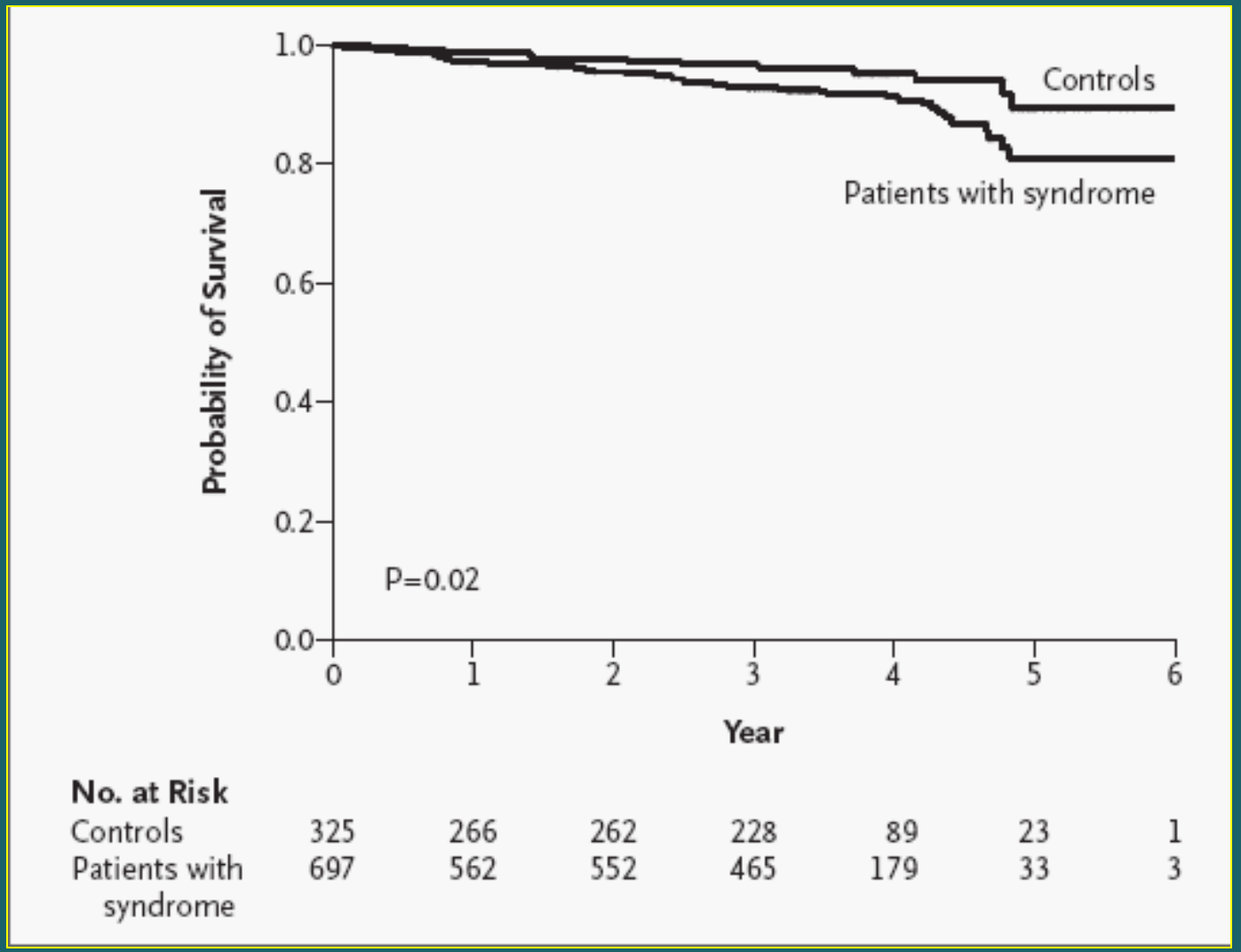


No. at Risk							
Controls	325	266	260	227	88	23	1
Patients with syndrome	697	559	543	452	173	33	3

Figure 1. Kaplan–Meier Estimates of the Probability of Event-free Survival among Patients with the Obstructive Sleep Apnea Syndrome and Controls.

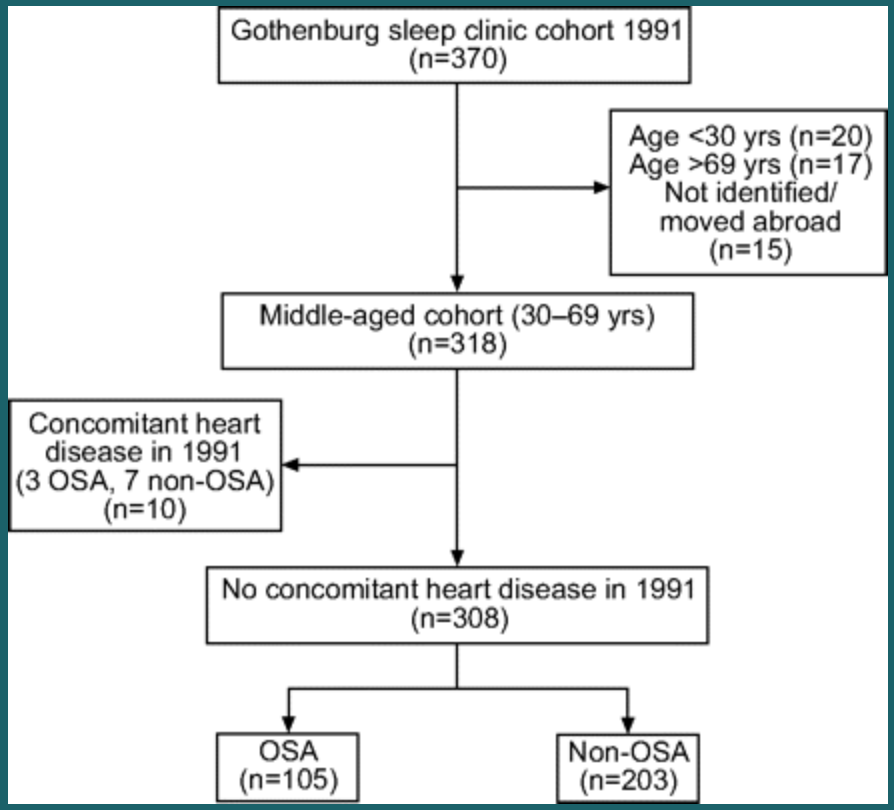
(Yaggi HK NEJM 2005)

OSA after stroke and the Probability of Death



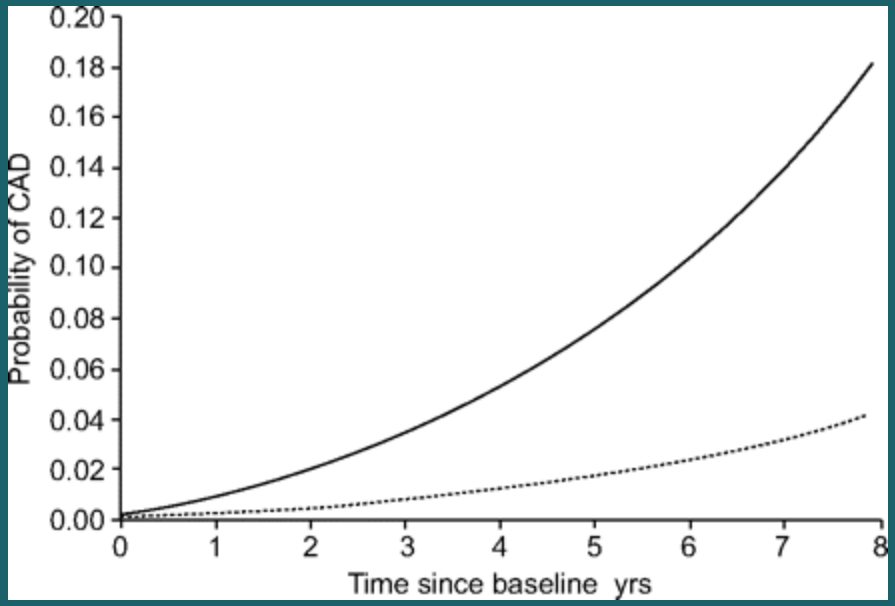
(Yaggi HK NEJM 2005)

Increased incidence of coronary artery disease in sleep apnea



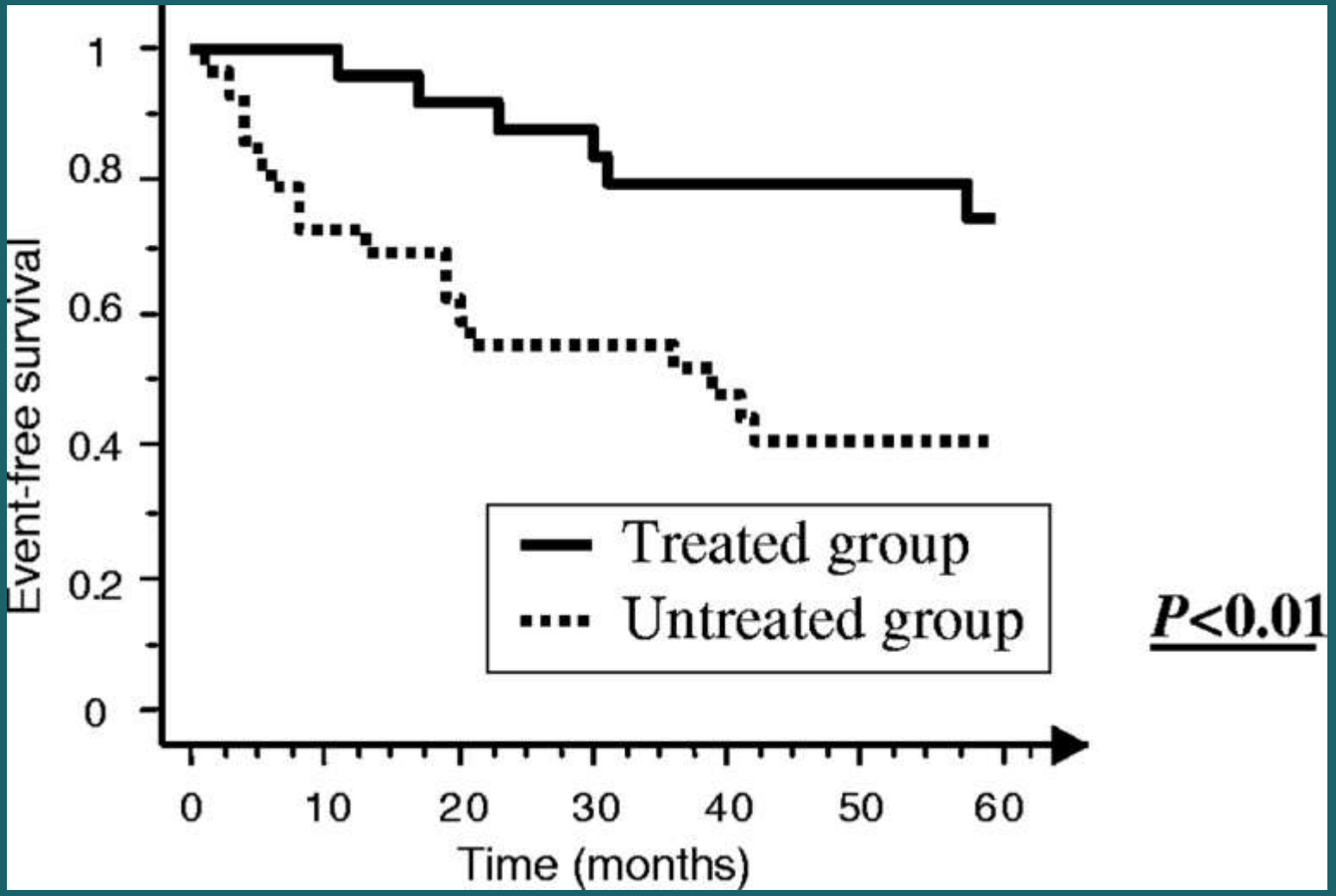
Peker et al Eur Resir J 2006

Increased incidence of coronary artery disease in sleep apnea



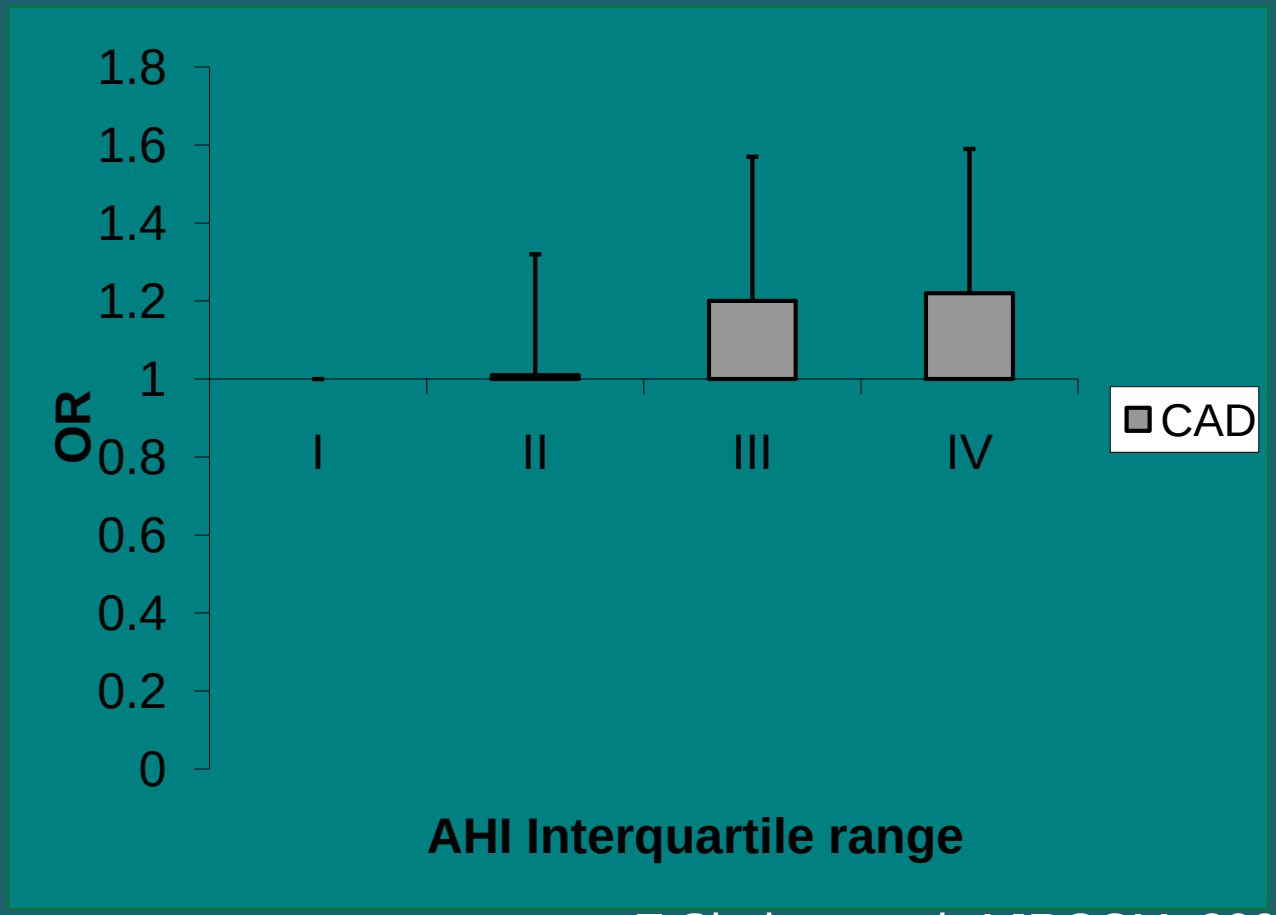
Peker et al Eur Resir J 2006

CAD and Treatment of OSA



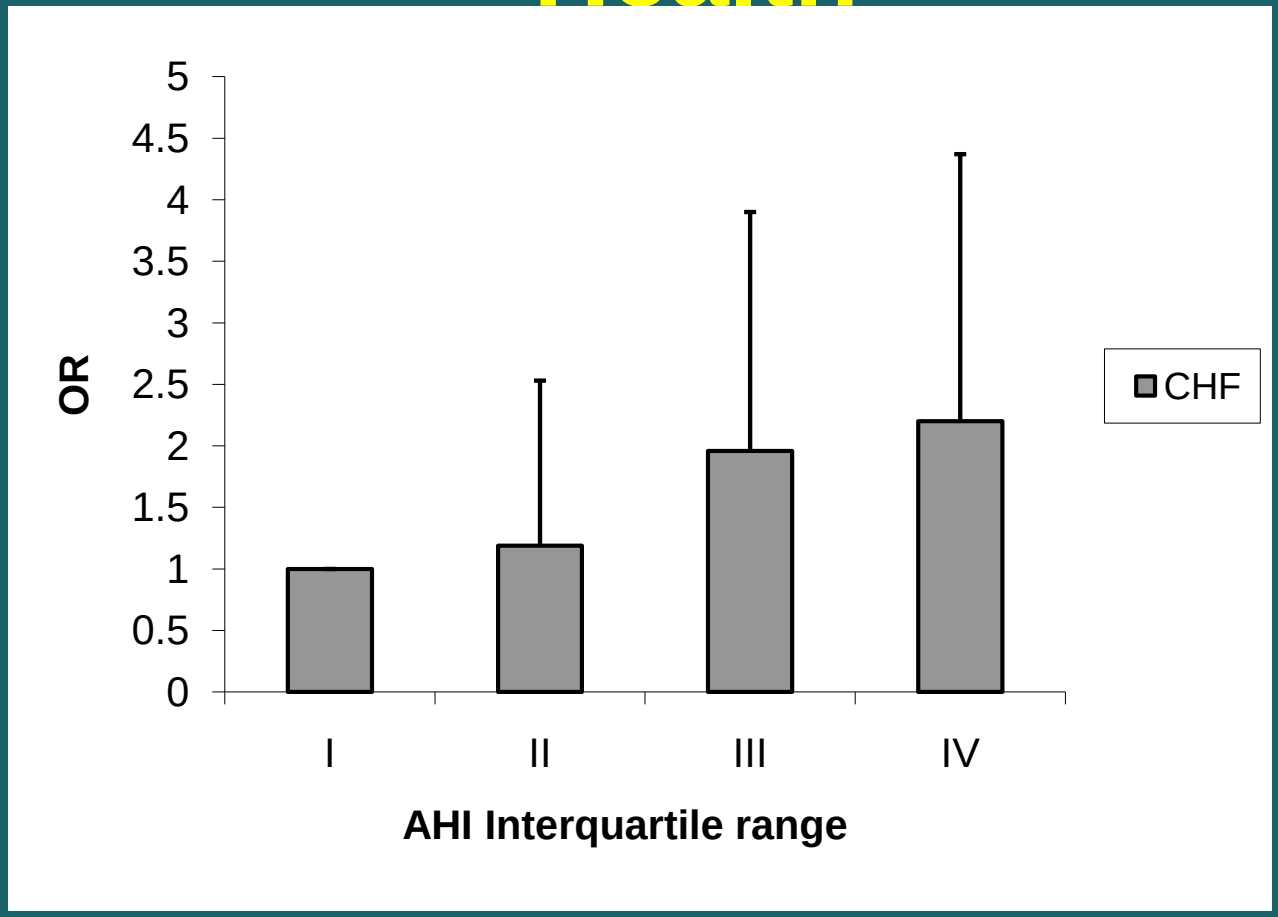
Milleron, O. et al. Eur Heart J 2004 25:728-734; doi:10.1016/j.ehj.2004.02.008

OSA and CAD-The Sleep Heart Health Study



E Shahar, et al, AJRCCM, 2001

OSA and CHF-the Sleep Heart Health



n=6,424

E Shahar, et al, AJRCCM, 2001

Atrial Fibrillation and OSA

- Prevalence of OSA in patients with A fib is higher than other patients of cardiology practice
- Association in Sleep Heart Health Study
- Association between OSA and recurrence of A fib following cardioversion
- Impact of OSA on atrial electromechanical activation time
  - Kanagola et al, Circ 107:2589, 2003
  - Gami et al, Circ 110(4):364-7, 2004
  - Lim et al circ r 2009

Association Between Severe OSA (AHI >30) and Arrhythmias in Sleep Heart Health Study

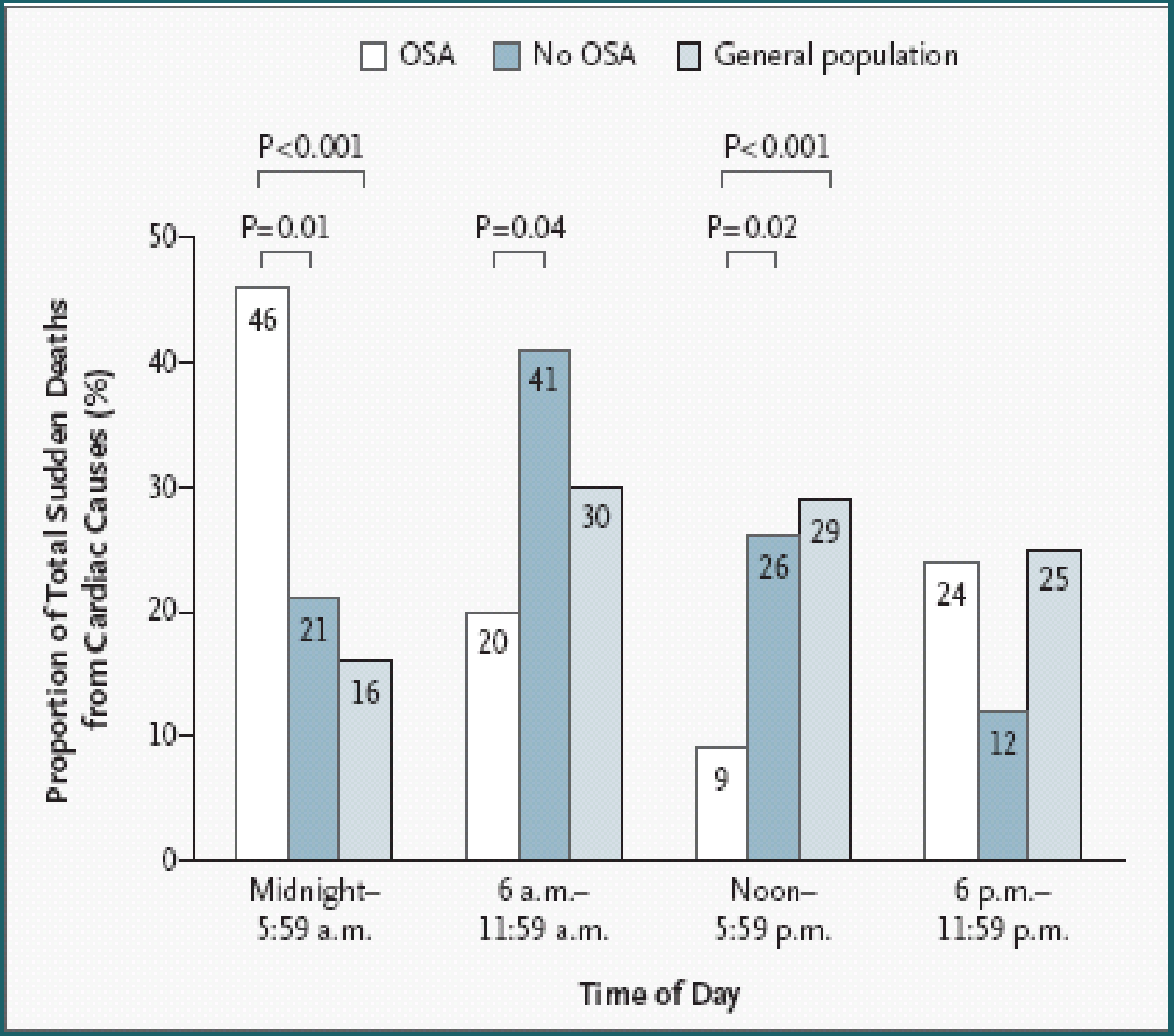
(Mehra et al, AJRCCM, doi:10.1164/rccm.200509-1442OC)

Arrhythmia Type	Unadjusted Odds Ratio	Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI	Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI, CHD
Non-sustained ventricular tachycardia	4.64 (1.48-14.57)	3.72 (1.13-12.2)	3.40 (1.03-11.2)
Complex ventricular ectopy	1.96 (1.28-3.00)	1.81 (1.16-2.84)	1.74 (1.11-2.74)
Atrial fibrillation	5.66 (1.56-20.52)	3.85 (1.00-14.93)	4.02 (1.03-15.74)

BMI=body mass index; CHD=coronary heart disease

*Results of logistic regression analysis with SDB as the exposure; N=338 without SDB, N=228 with SDB

Sudden Cardiac Death in OSA



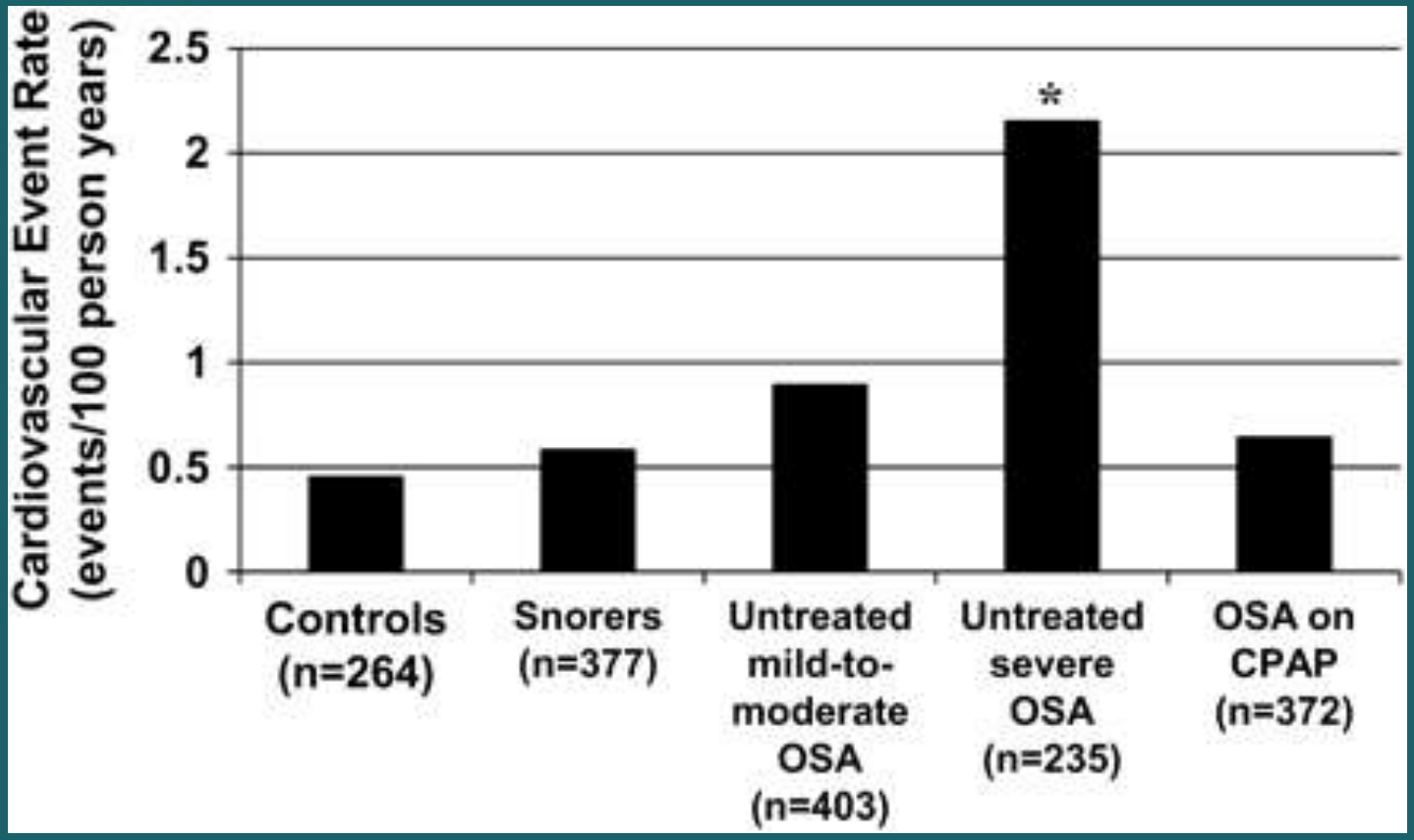
N Engl J Med 2005;352:1206-14.

OSA and Cardiovascular Disease

- OSA is present in at least 10-25% of patients 30-60 years
- Prevalence increases with obesity and aging- both risk factors for heart failure
- OSA is a cause of hypertension and a risk factor for CAD the most common causes of heart failure
- OSA is present in up to 60% of patients with heart failure
- Adams et al (ADHERE)Am Heart J, 2005
- Nieminen (EHFS II) Eur Heart J, 2006
- Khayat 2009, Pauline 2009

Causative Role of Severe Untreated OSA in Cardiovascular Events

(Marin et al, Lancet 365:1046, 2005)

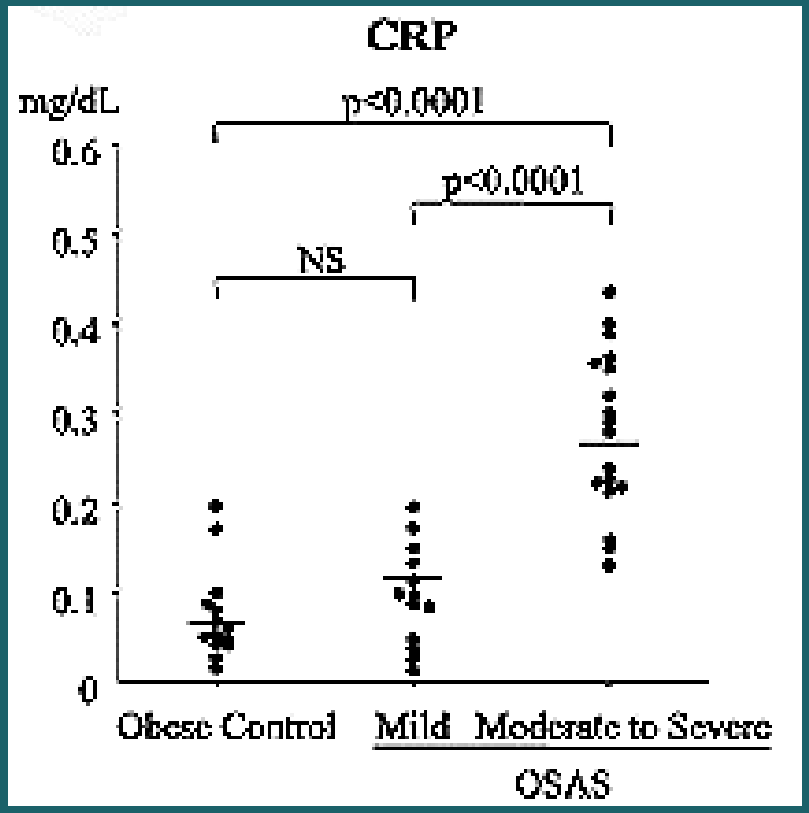


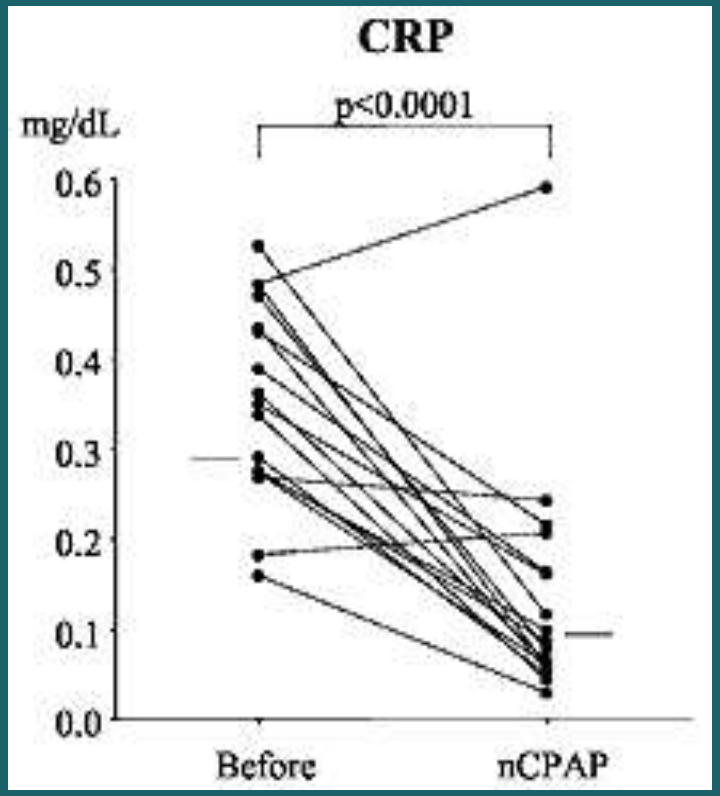
OSA is a Cardiovascular Risk Factor

- OSA is a cardiovascular risk factor just like high cholesterol and diabetes
  - Certain cardiovascular risk factors are modifiable
  - Early identification and treatment of cardiovascular risk factors is the current focus of care
  - Treatment of co-existent OSA in patients with established heart disease is critical

C-Reactive Protein is Increased in Moderate to Severe Sleep Apnea

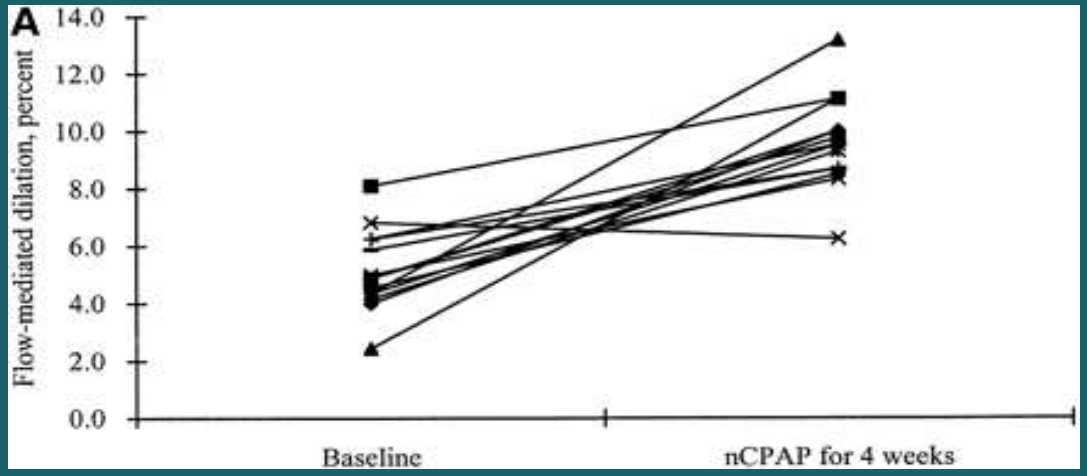
(Yokoe et al, Circulation 107:1129, 2003)



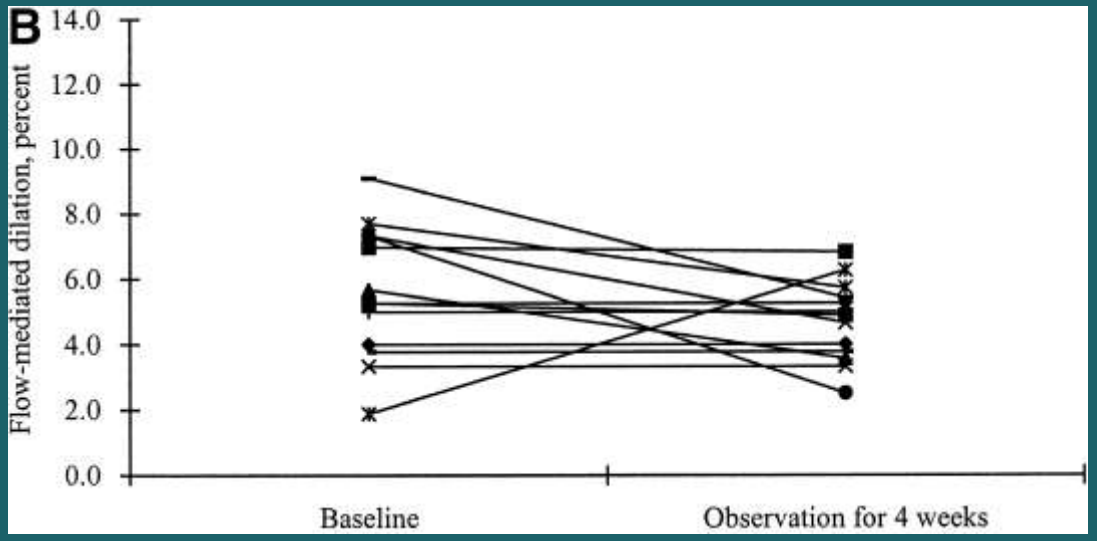


Endothelial Dysfunction in OSA

Ip et al 2003 AJRCC

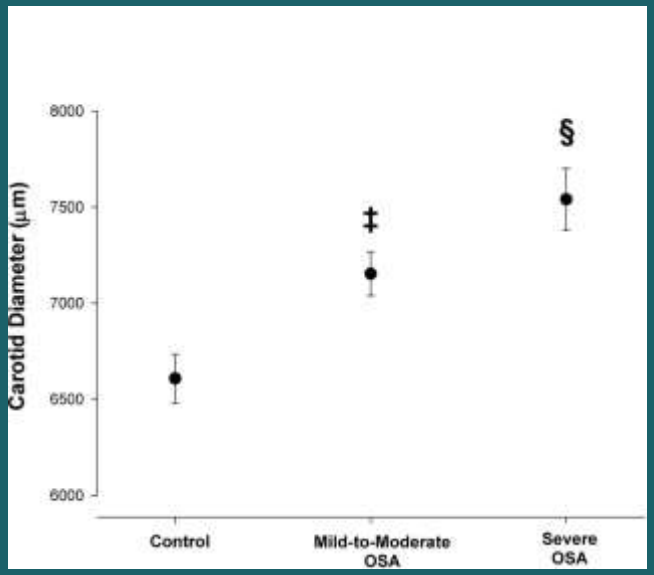


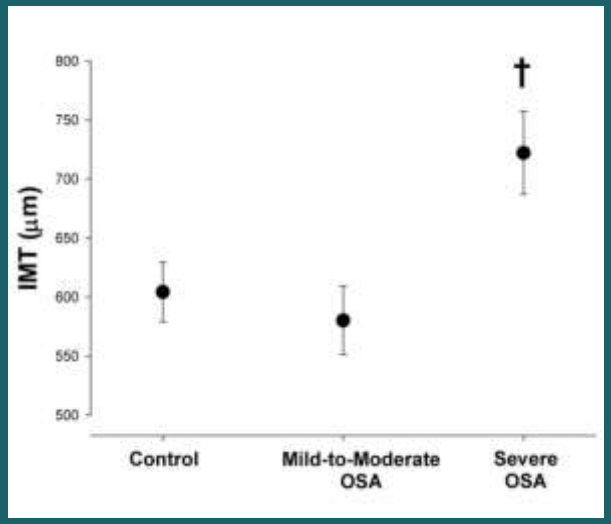
A) FMD of brachial artery in 14 subjects with OSA at baseline and after 4 weeks of (n CPAP) (p = 0.001).

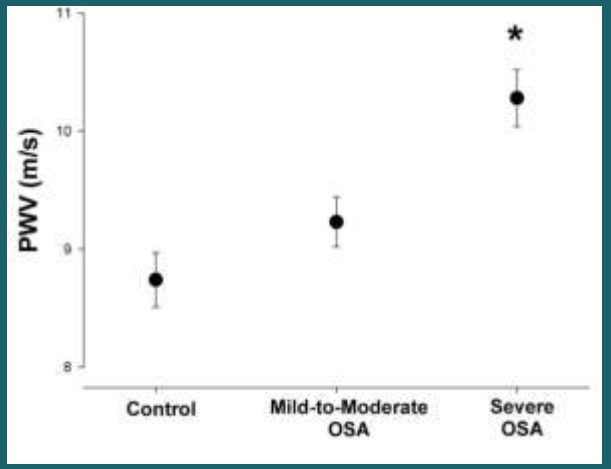


B) FMD of brachial artery in 13 subjects with OSA at baseline and after 4 weeks of observation (p = 0.12).

Effects of OSA on Atherosclerosis

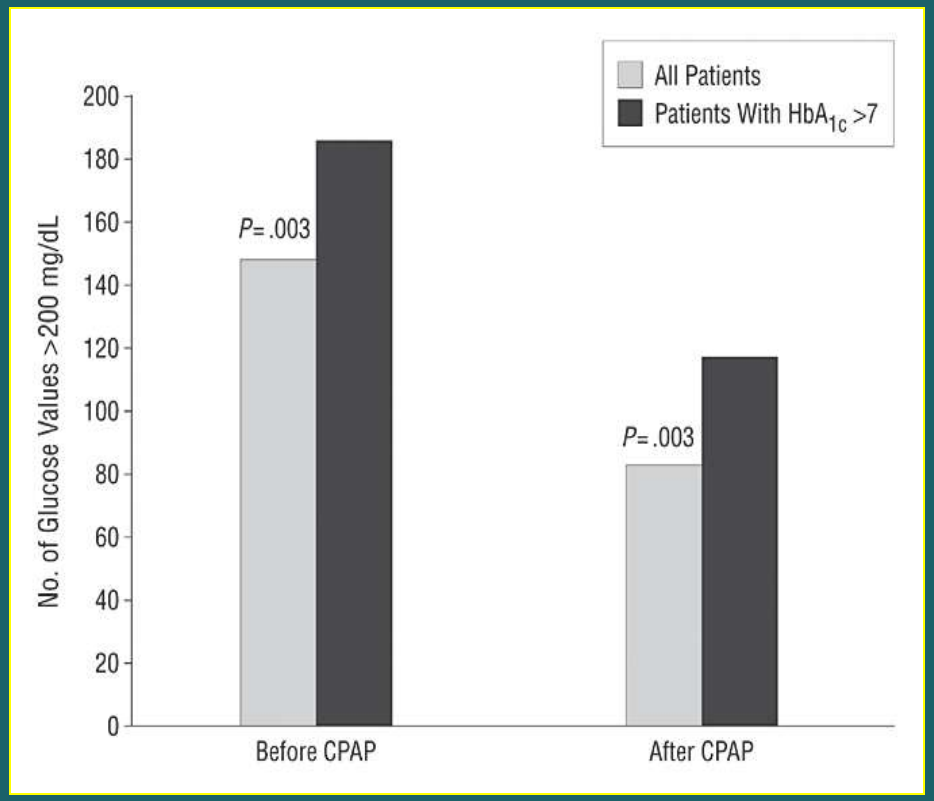




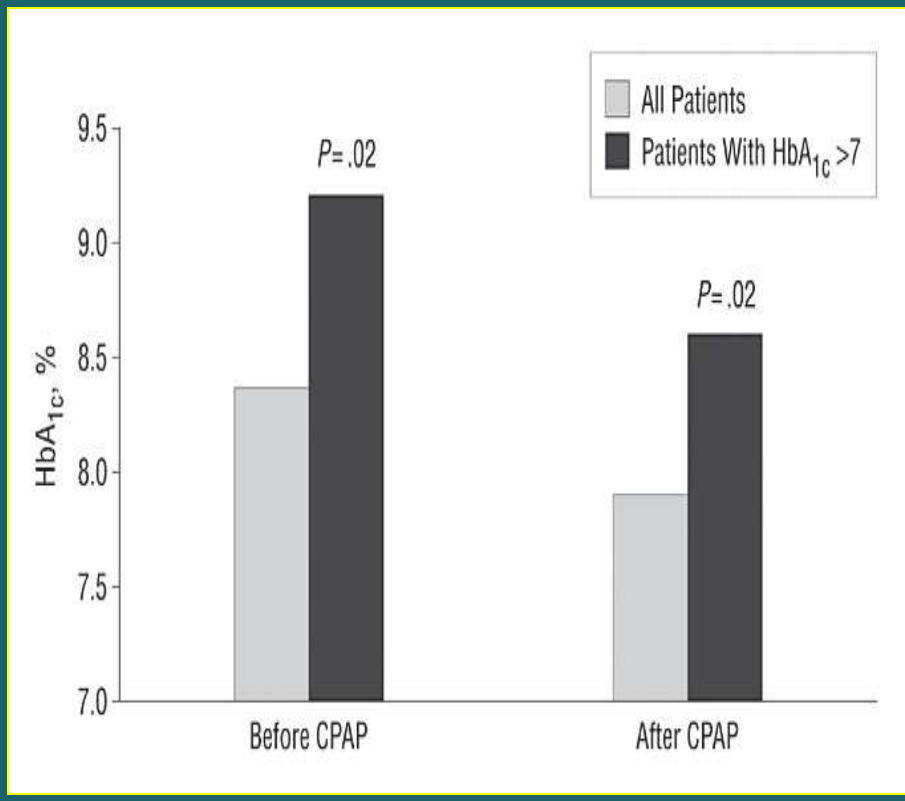


Drager et al AJRCC 2005

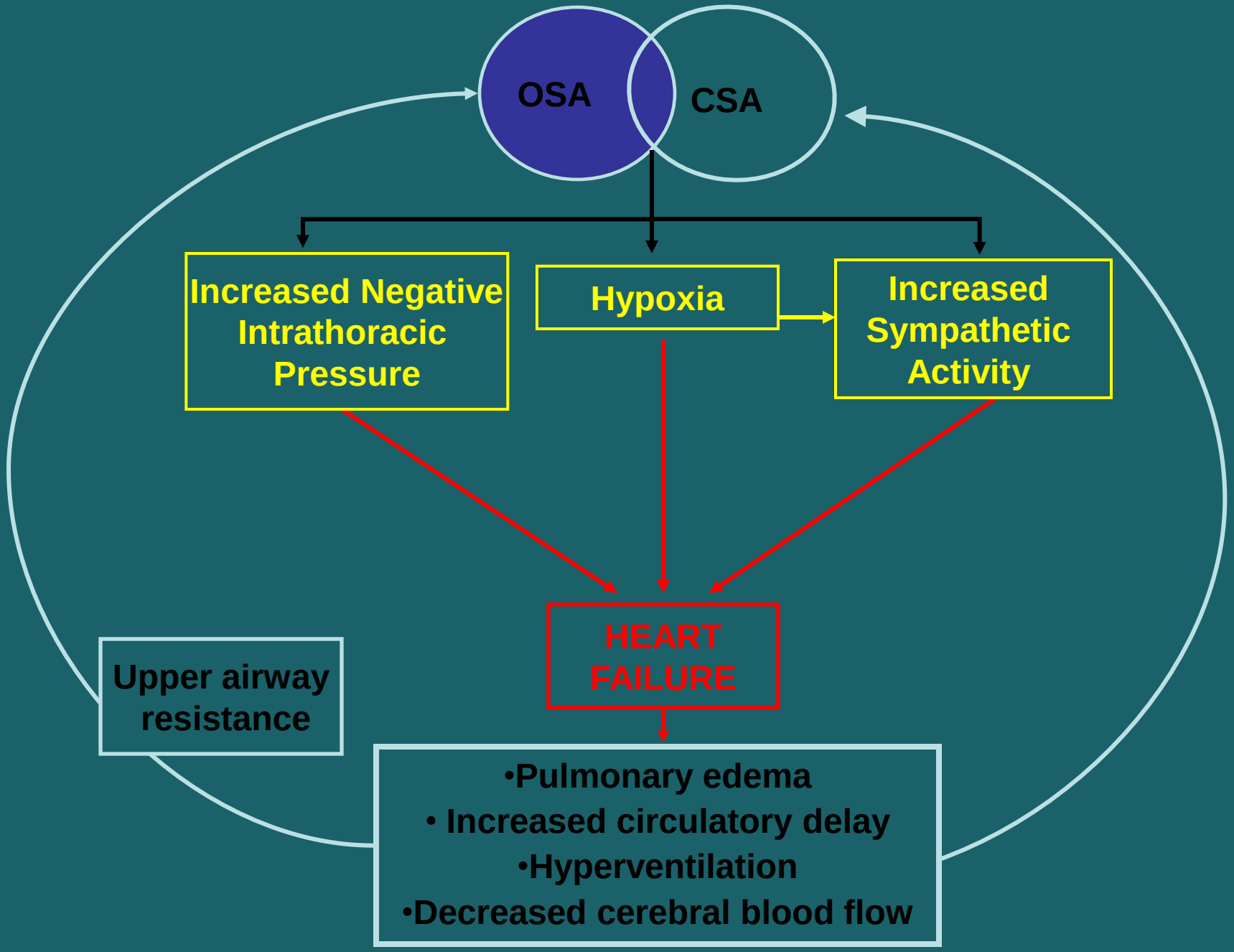
Change in Glucose with CPAP



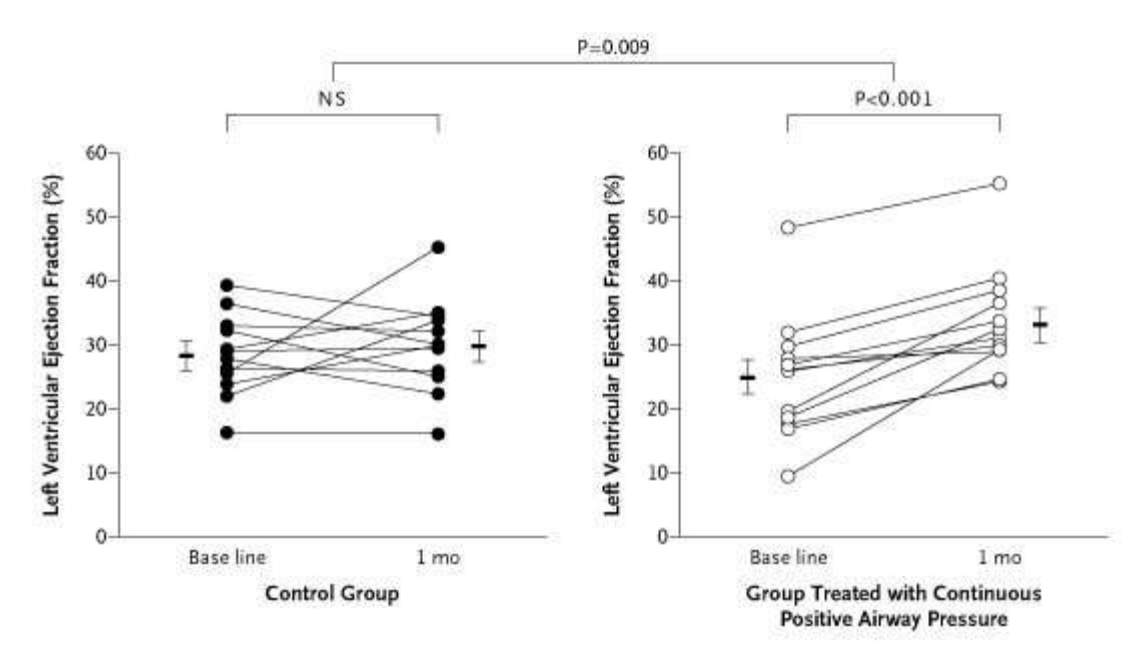
Change in HbA1c with CPAP



(Babu Arch Intern Med 2005)

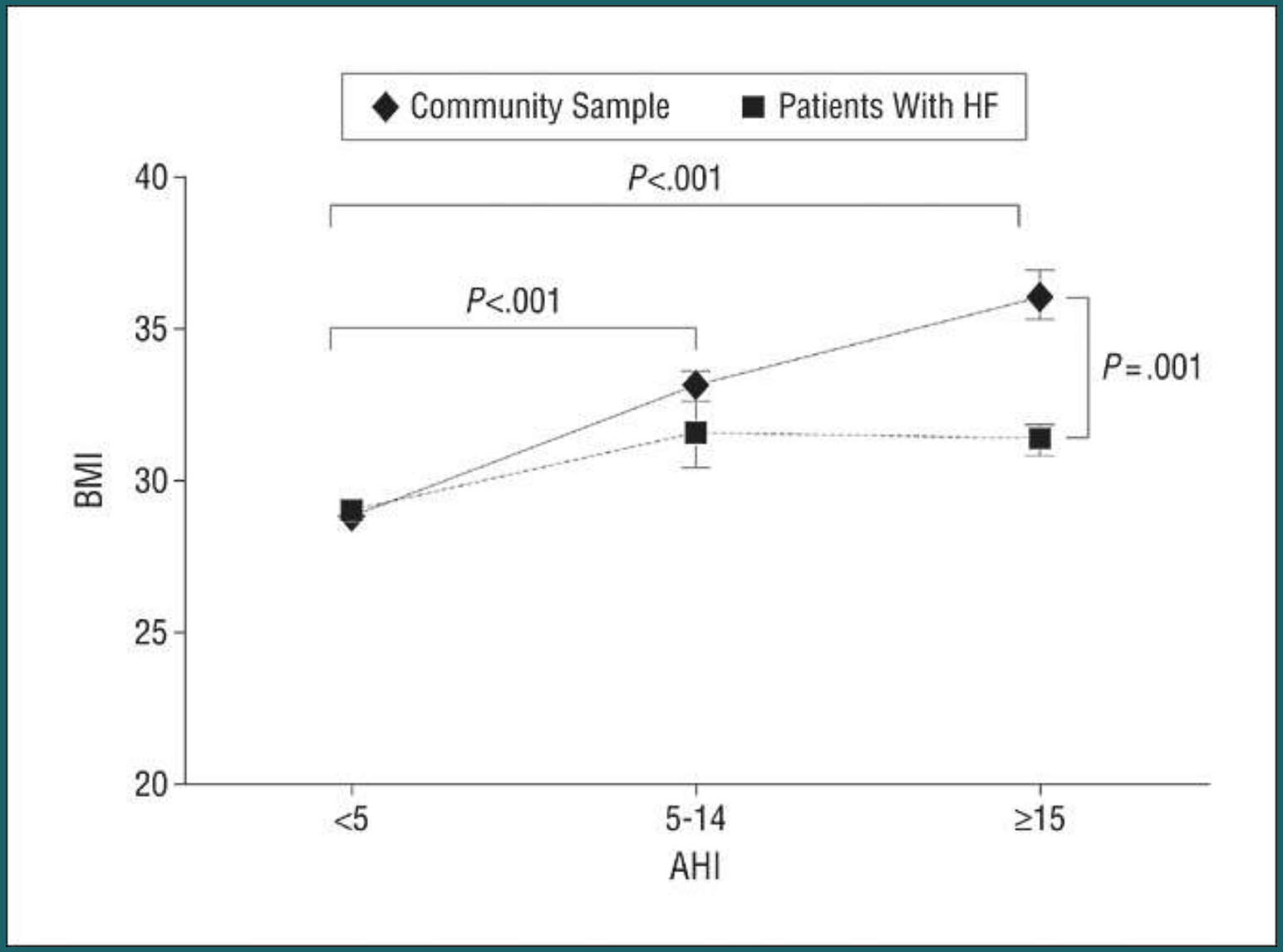

OSA
CSA
Increased Negative Intrathoracic Pressure
Hypoxia
Increased Sympathetic Activity
HEART FAILURE
Upper airway resistance
•Pulmonary edema
• Increased circulatory delay
•Hyperventilation
•Decreased cerebral blood flow

CPAP improves LVEF in patients with CHF



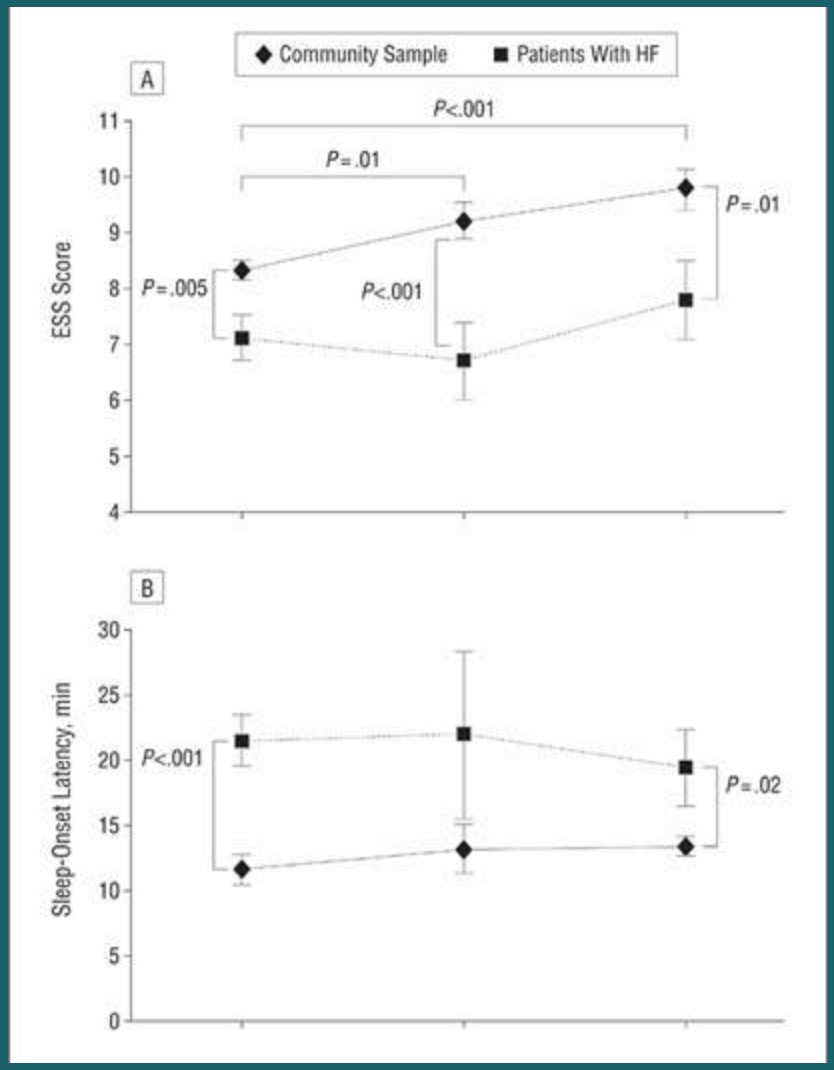
Kaneko, N Engl J Med 2003

OSA- Presentation in Heart Failure

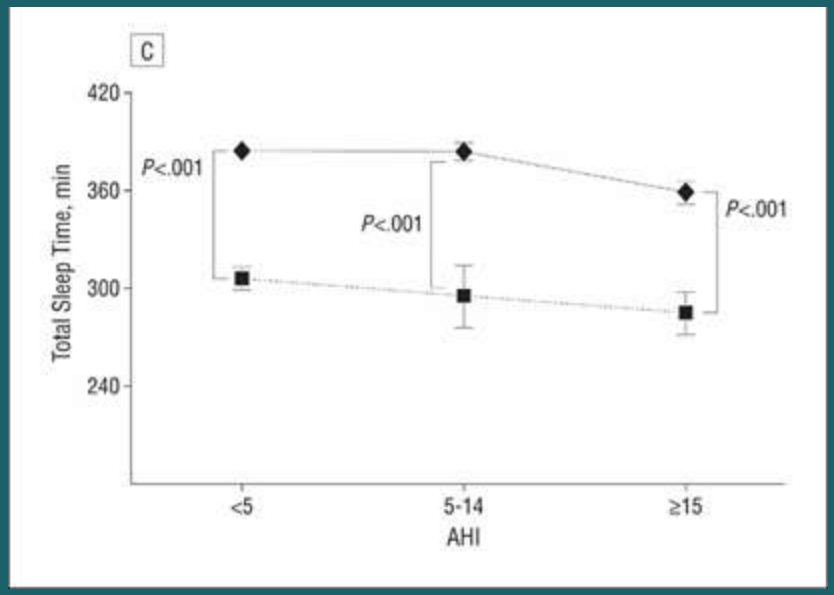


Arzt, M. et al. Arch Intern Med 2006;166:1716-1722.

OSA- Presentation in Heart Failure

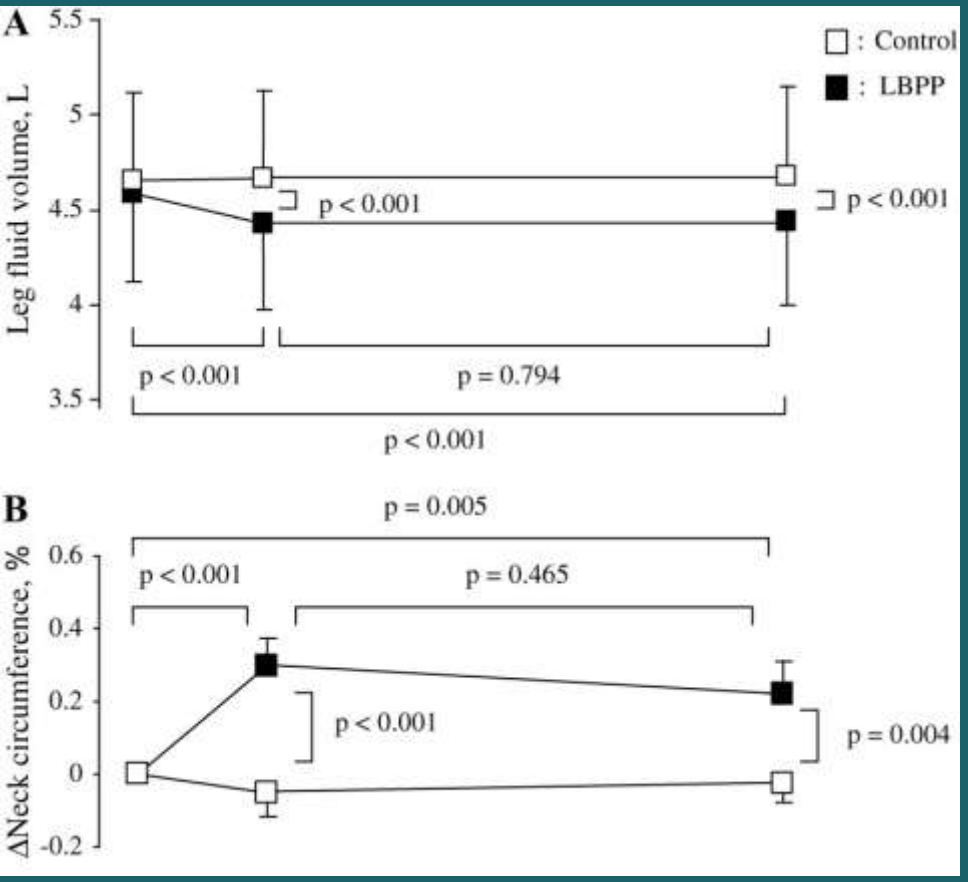


Epworth Sleepiness Scale (ESS) score and sleep structure by apnea-hypopnea index (AHI) categories (<5, 5-14, and ≥15)

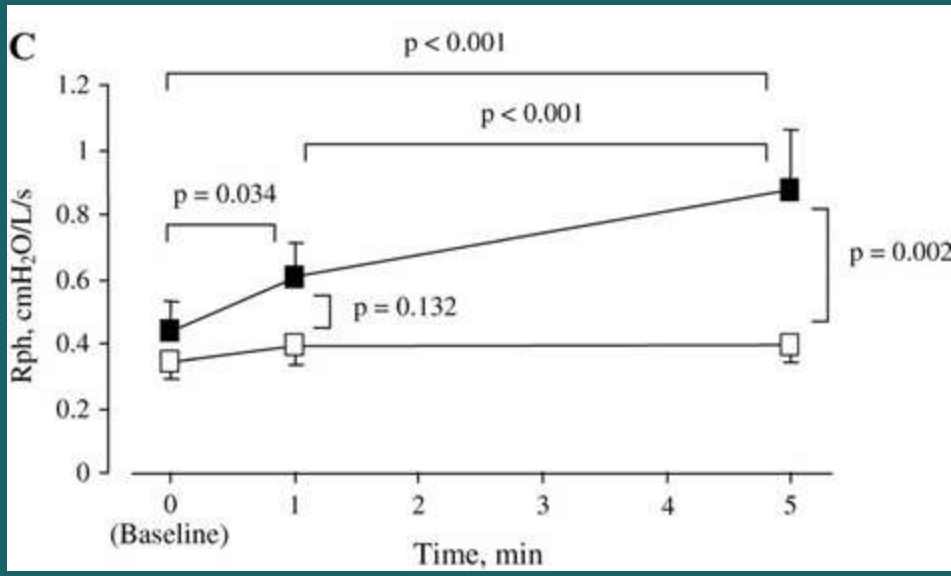


Arzt, M. et al. Arch Intern Med 2006;166:1716-1722.

Mechanism of OSA in Heart Failure

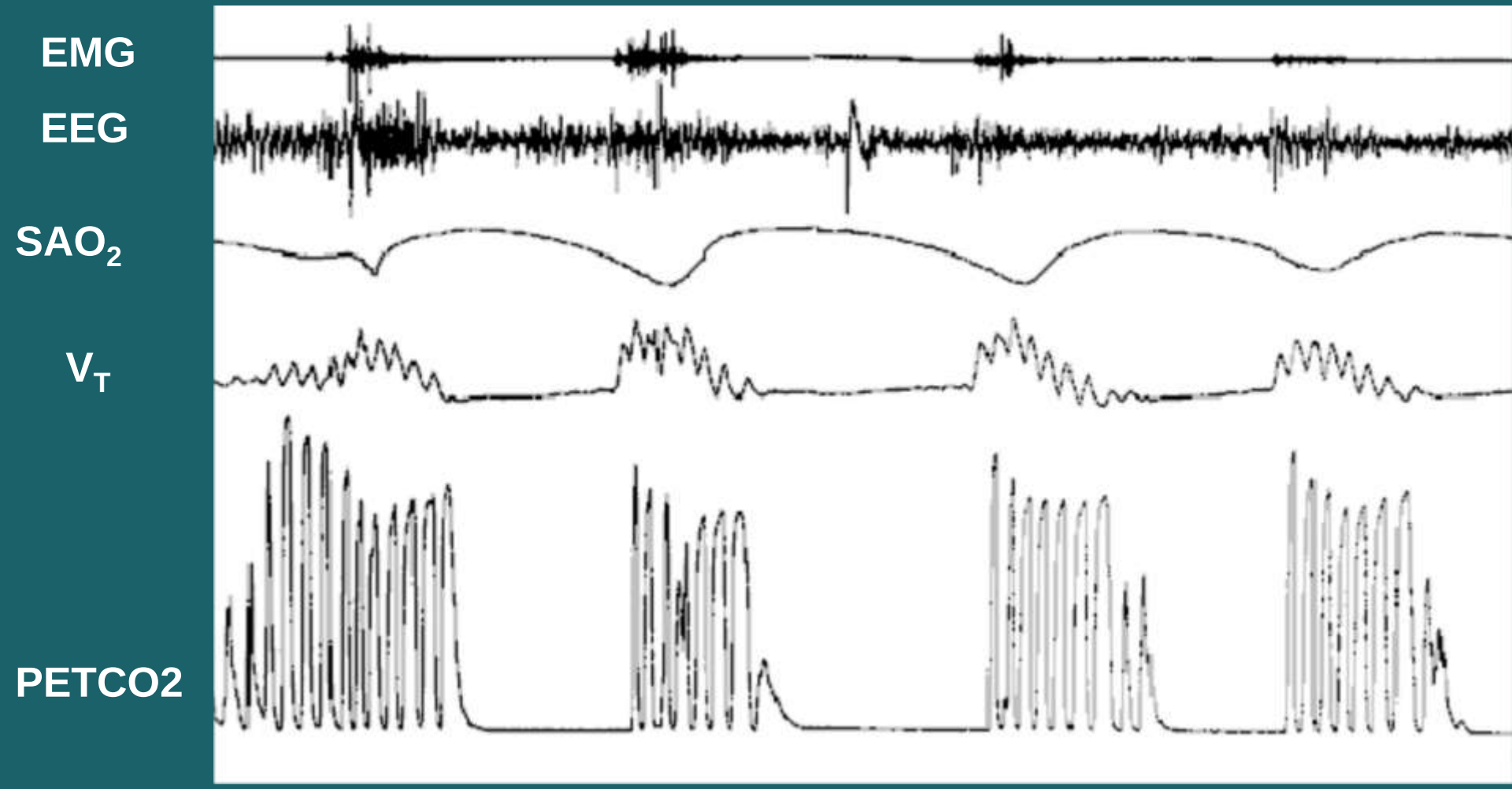


Fluid Shift and Pharyngeal Resistance in Healthy Subjects

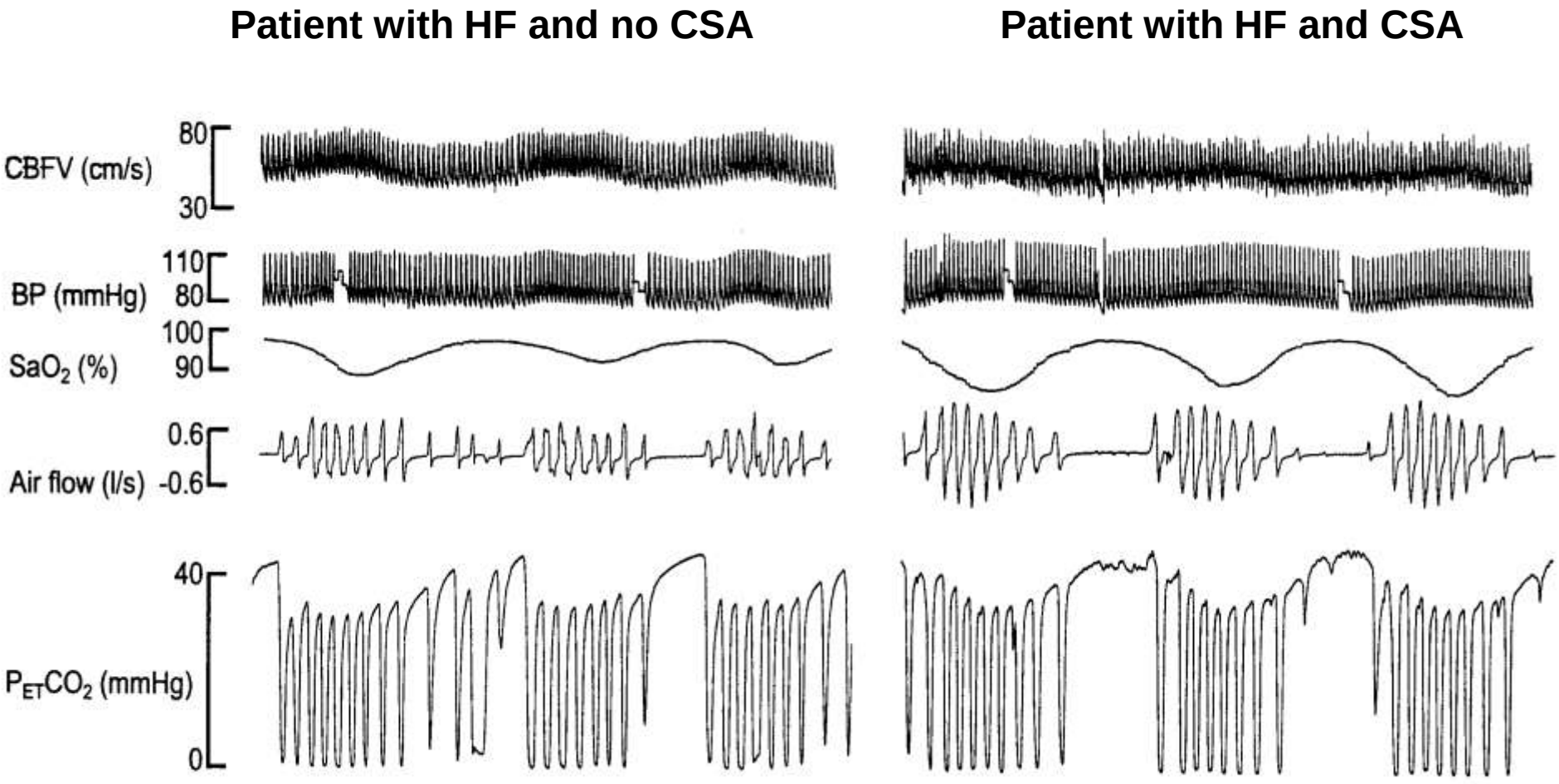


Cheu et al AJRCC 2006

Central Sleep Apnea in Heart Failure-Cheyne Stokes respiration



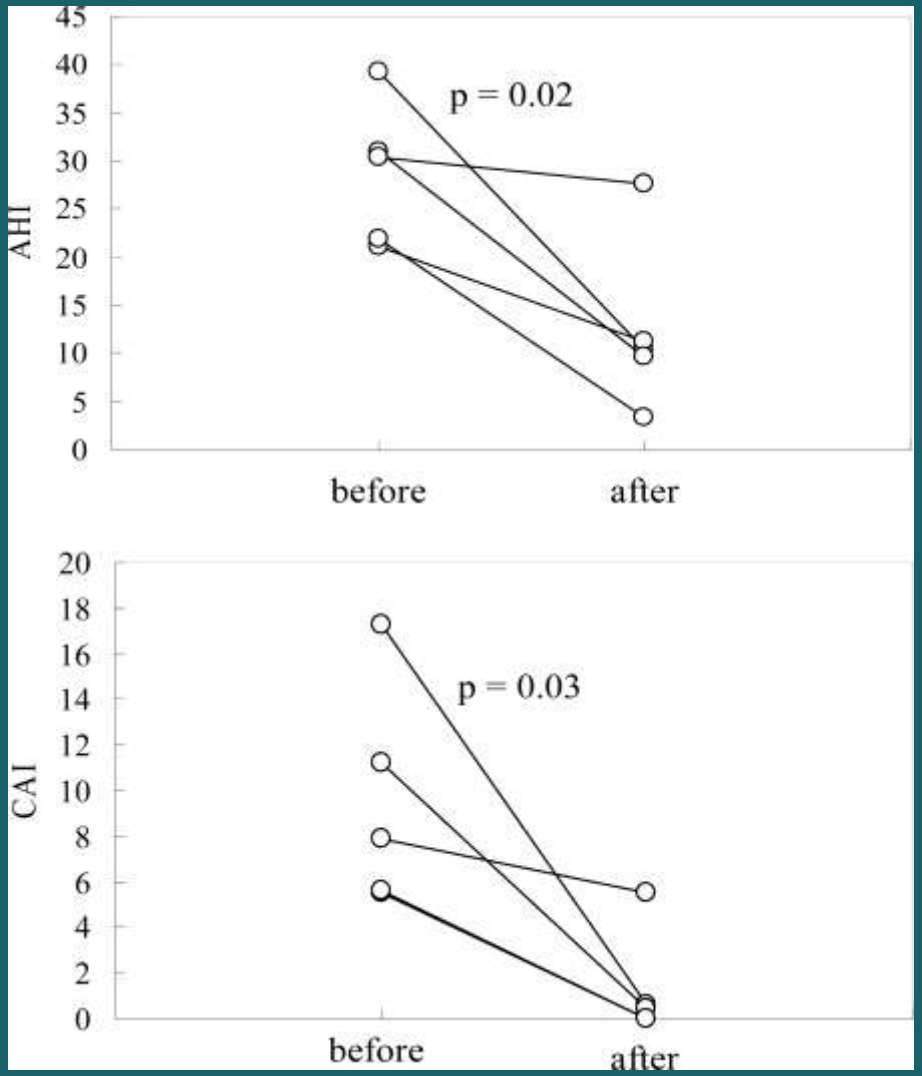
Induced Periodic Breathing and CBFV in CHF



Xie et al 2005

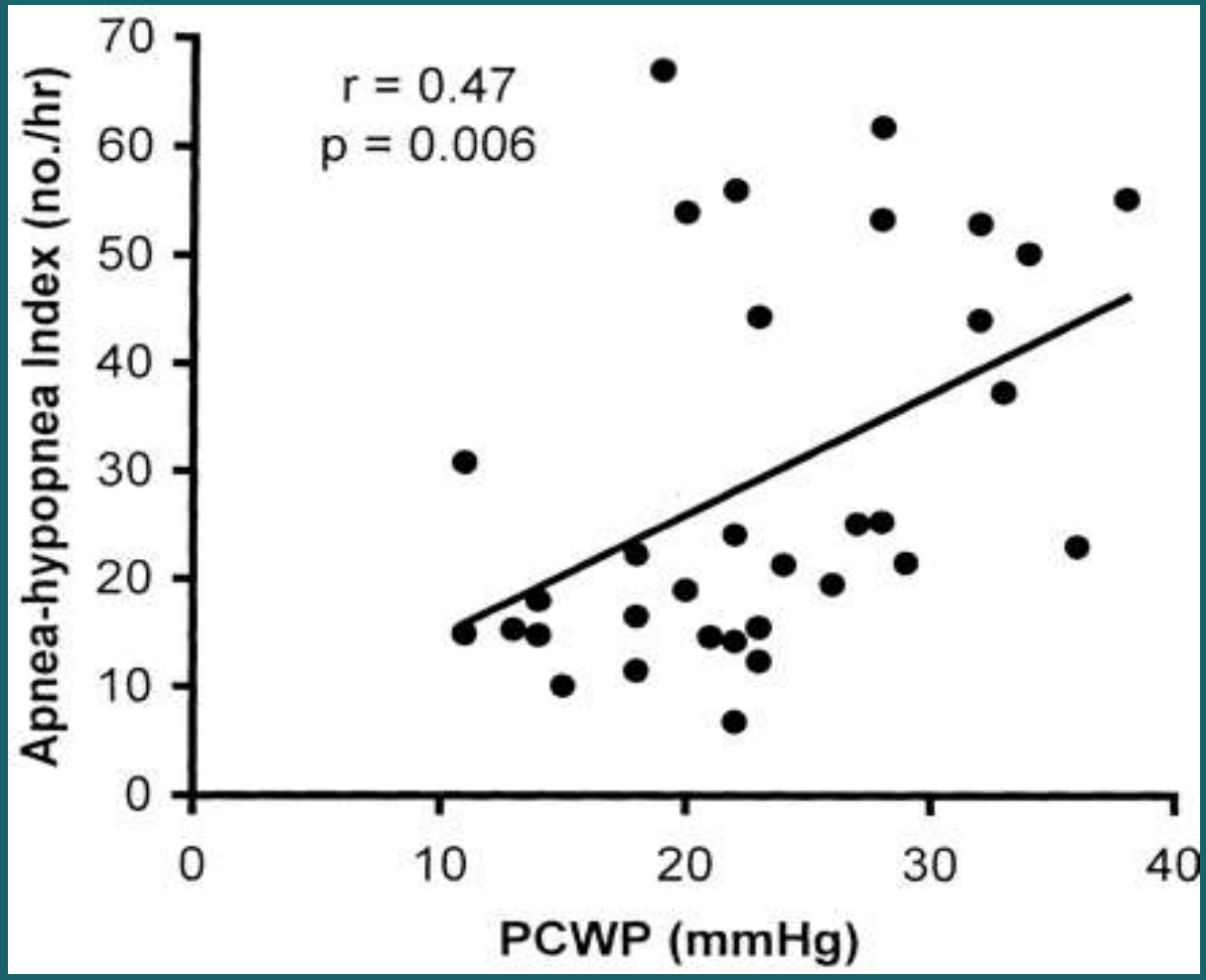
Central Sleep Apnea and b Blockers

Tamura, A. et al. Chest 2007;131:130-135



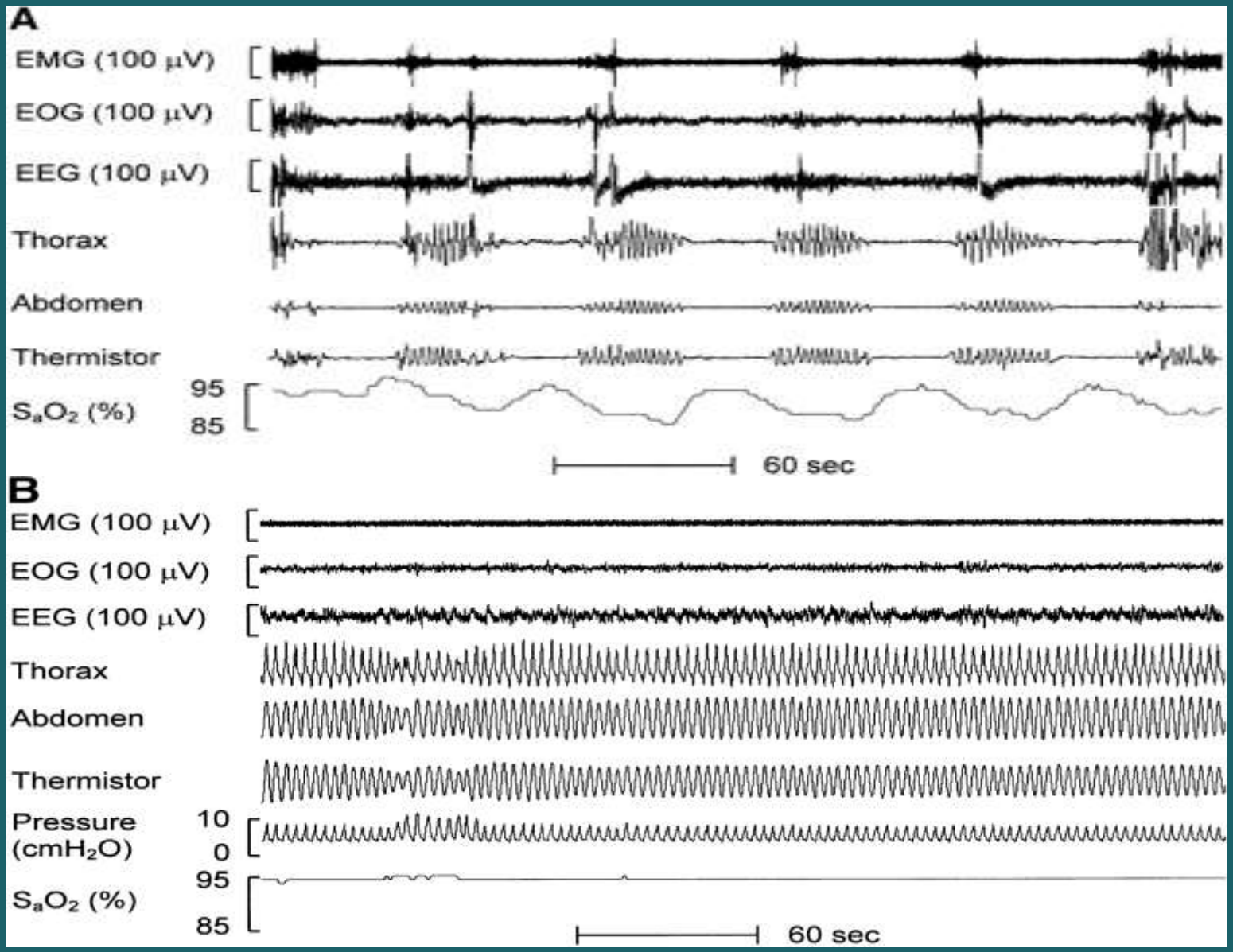
Changes in AHI and CAI before and 6 months after induction of carvedilol in five patients with CAI > 5 at baseline

Relation between PCWP and AHI in Patients with HF and CSA: Effect of Optimal CHF Management on CSA

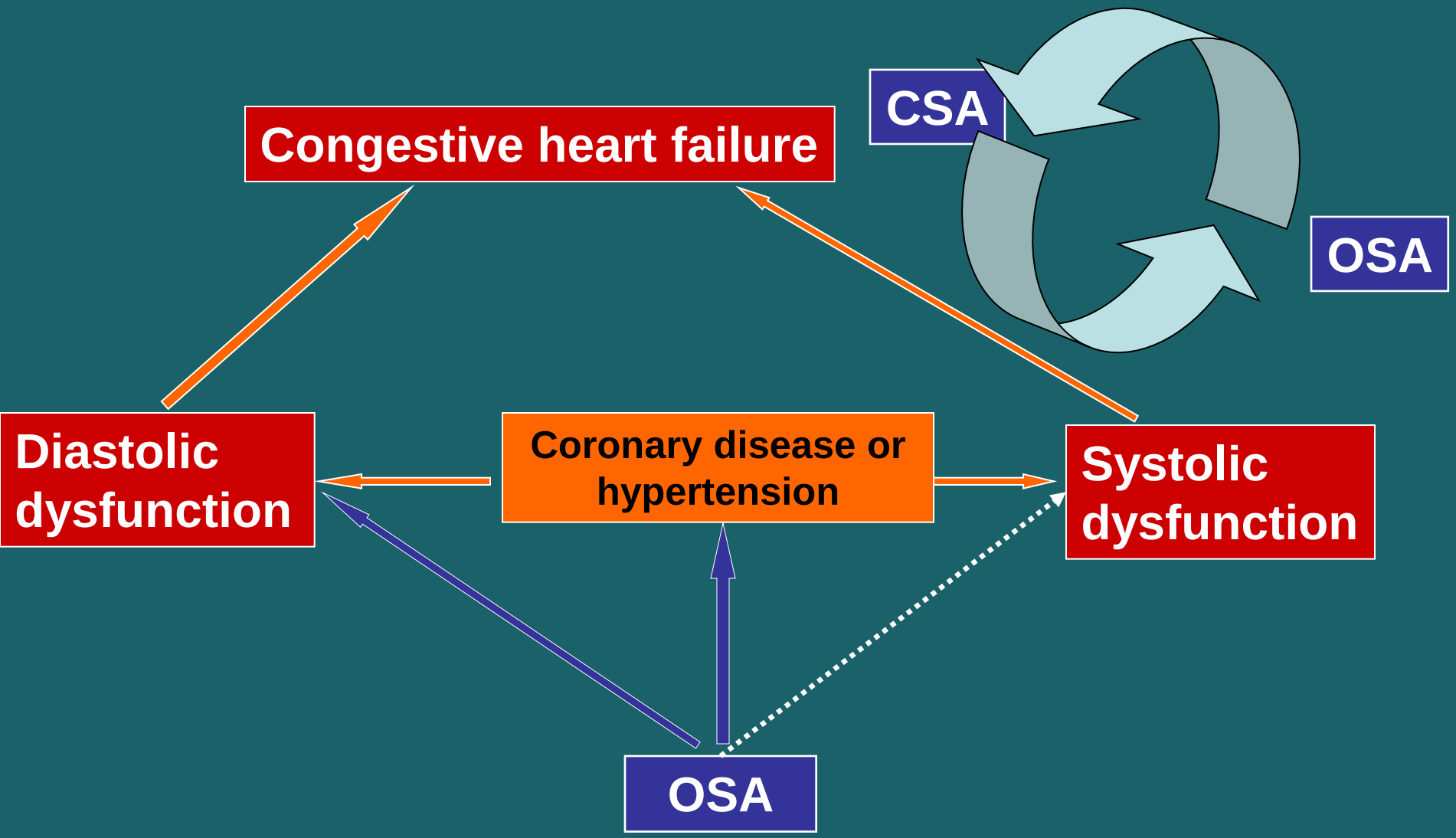


Naughton et al 1999

Treatment of CSA with Adaptive Servo Ventilation- Teschler et al AJRCC2001

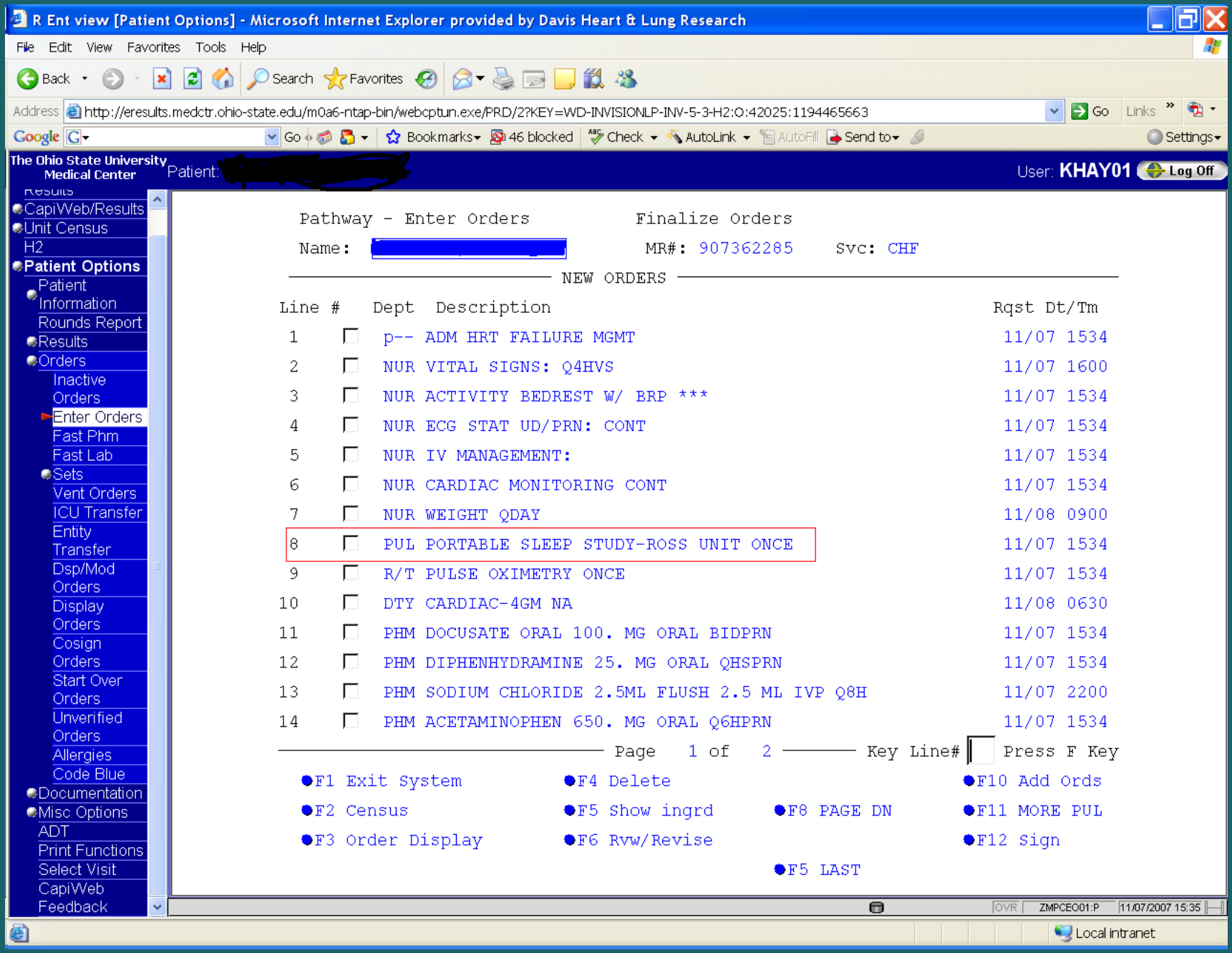


SBD and Heart Failure in Clinical Practice



If SDB is highly prevalent in patients with heart failure, and it worsens outcomes, why are we not routinely screening for it?

- **Criteria for case finding:**
- **Highly prevalent disorder**
- **Known negative impact**
- **Treatable disorder**
- **Feasibility of identification**
  - **WHO 1966- Jungner**


R Ent view [Patient Options] - Microsoft Internet Explorer provided by Davis Heart & Lung Research
File Edit View Favorites Tools Help
Back Search Favorites
Address http://eresults.medctr.ohio-state.edu/m0a6-ntap-bin/webcptun.exe/PRD/2?KEY=WD-INVISIONLP-INV-5-3-H2:O:42025:1194465663
Go Links
Google Go Bookmarks 46 blocked Check AutoLink AutoFill Send to Settings
The Ohio State University Medical Center
Patient: [redacted]
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Results
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Patient Information
Rounds Report
Results
Orders
Inactive Orders
Enter Orders
Fast Phm
Fast Lab
Sets
Vent Orders
ICU Transfer
Entity Transfer
Dsp/Mod Orders
Display Orders
Cosign Orders
Start Over Orders
Unverified Orders
Allergies
Code Blue
Documentation
Misc Options
ADT
Print Functions
Select Visit
CapiWeb Feedback
Pathway - Enter Orders Finalize Orders
Name: [redacted] MR#: 907362285 Svc: CHF
NEW ORDERS
Line # Dept Description Rqst Dt/Tm
1 p-- ADM HRT FAILURE MGMT 11/07 1534
2 NUR VITAL SIGNS: Q4HVS 11/07 1600
3 NUR ACTIVITY BEDREST W/ BRP *** 11/07 1534
4 NUR ECG STAT UD/PRN: CONT 11/07 1534
5 NUR IV MANAGEMENT: 11/07 1534
6 NUR CARDIAC MONITORING CONT 11/07 1534
7 NUR WEIGHT QDAY 11/08 0900
8 PUL PORTABLE SLEEP STUDY-ROSS UNIT ONCE 11/07 1534
9 R/T PULSE OXIMETRY ONCE 11/07 1534
10 DTY CARDIAC-4GM NA 11/08 0630
11 PHM DOCUSATE ORAL 100. MG ORAL BIDPRN 11/07 1534
12 PHM DIPHENHYDRAMINE 25. MG ORAL QHSPRN 11/07 1534
13 PHM SODIUM CHLORIDE 2.5ML FLUSH 2.5 ML IVP Q8H 11/07 2200
14 PHM ACETAMINOPHEN 650. MG ORAL Q6HPRN 11/07 1534
Page 1 of 2 Key Line# Press F Key
F1 Exit System
F2 Census
F3 Order Display
F4 Delete
F5 Show ingrd
F6 Rvw/Revise
F8 PAGE DN
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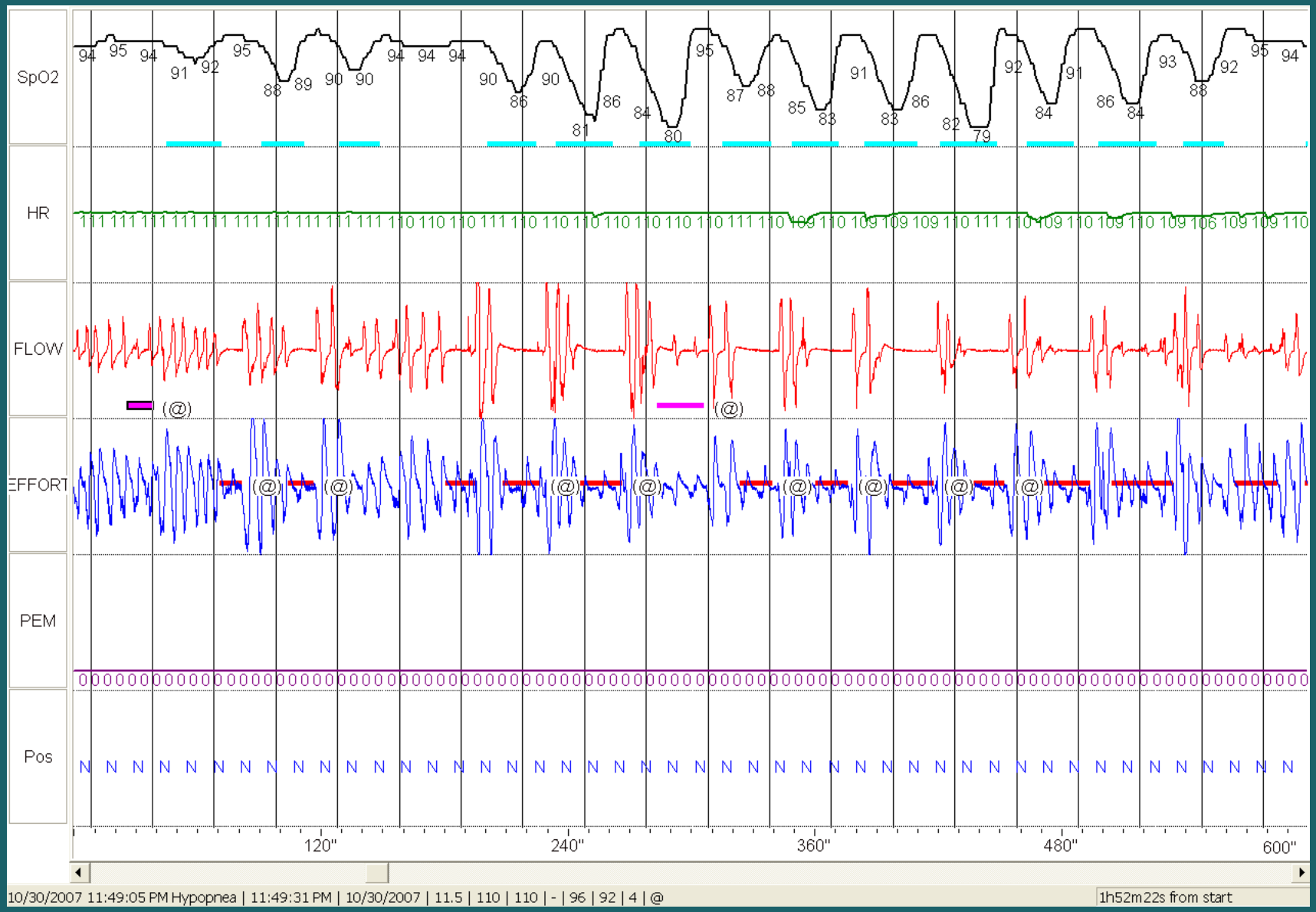
F10 Add Ords
F11 MORE PUL
F12 Sign
OVR ZMPCEO01:P 11/07/2007 15:35
Local intranet


SpO2
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120"
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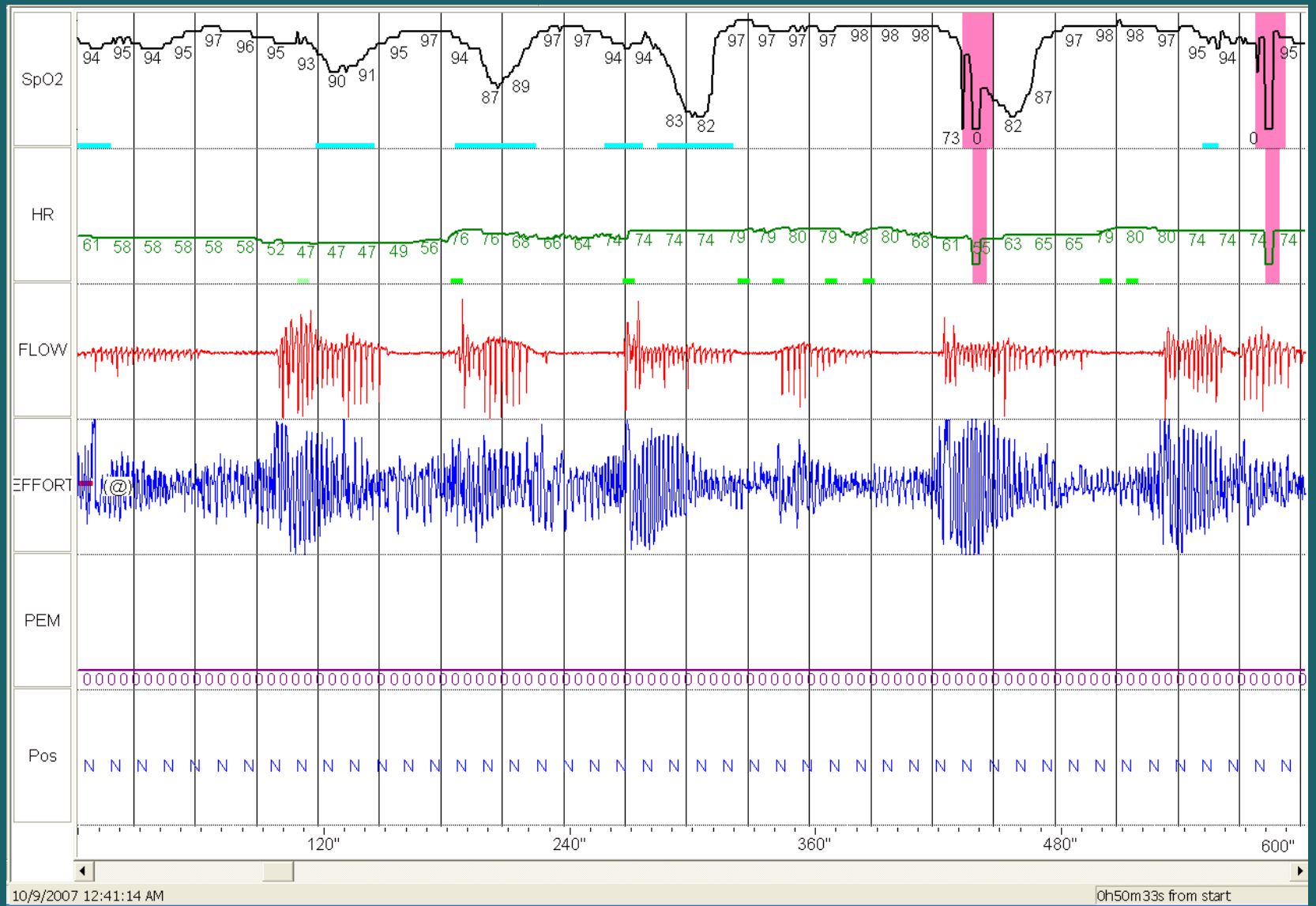
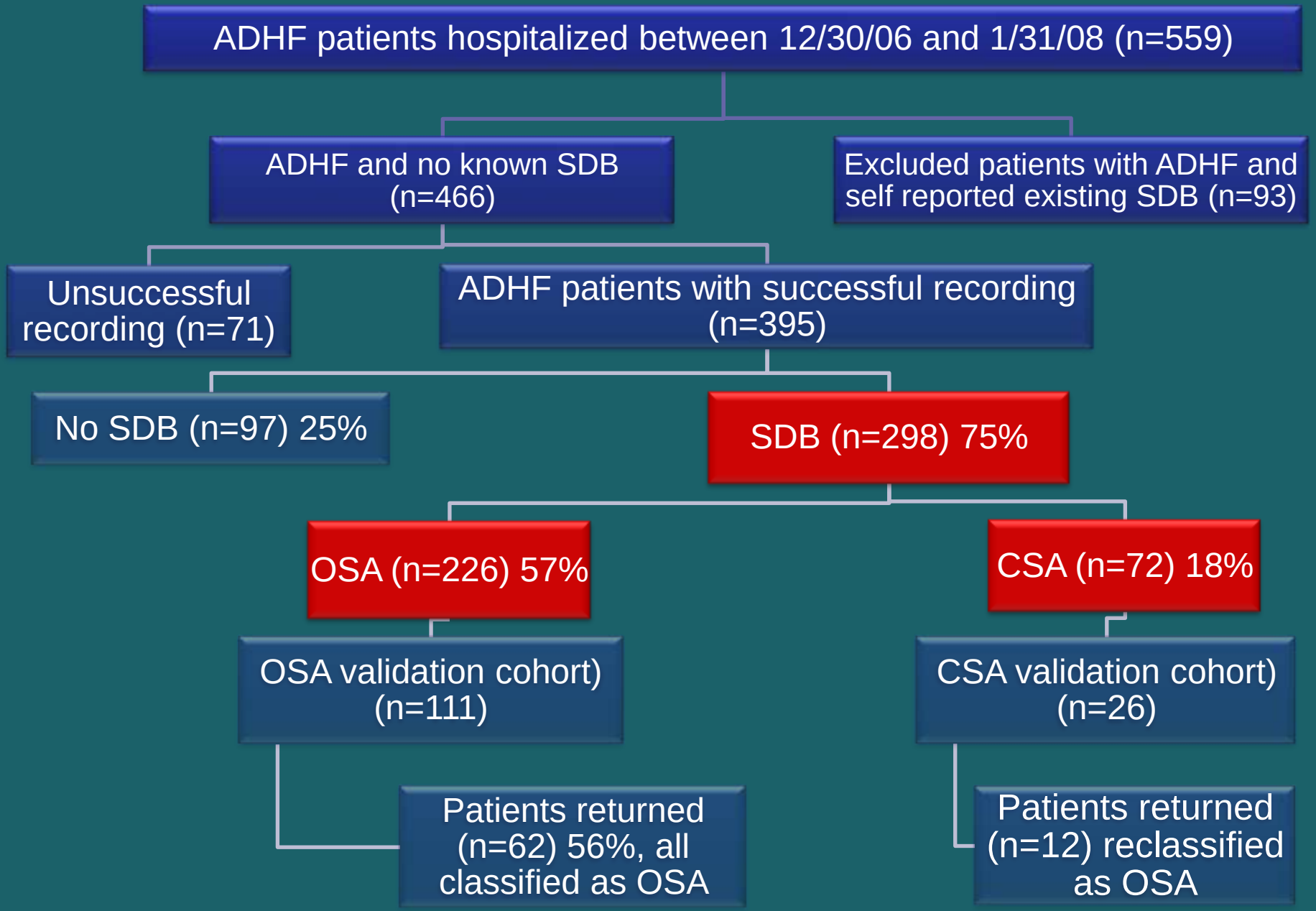
10/30/2007 11:49:05 PM Hypopnea | 11:49:31 PM | 10/30/2007 | 11.5 | 110 | 110 | - | 96 | 92 | 4 | @
1h52m22s from start

63 y/o OSA with long circulatory time





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Prevalence of OSA in ADHF Patients

- Patients admitted to the Ross hospital with ADHF
- Inpatients sleep studies on day 1-2 on all new admission
- No selection on part of treating physicians or nurses
- Automatic COE, Network and staff initiated studies

Characteristics of Patients with ADHF

Patient characteristic (number of Patients with data)	Mean or % (SE)	95% Confidence Interval
Age (395)	59 (0.7)	(57, 60)
Sex (male) (395)	62 % (2%)	(58 %, 67 %)
Ischemic cardiomyopathy (395)	57 (0.8)	(56, 59)
Left ventricular ejection fraction (370)	33 (0.9)	(32, 35)
BMI kg/cm2 (393)	32 (0.4)	(31, 33)
Admission BNP pg/mL (294)	888 (59)	(773, 1003)
Atrial fibrillation (394)	35 % (2%)	(30 %, 39 %)

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	OSA Mean (SE)	CSA Mean (SE)	Negative Mean (SE)	Negatives vs. OSA P value	Negative vs. CSA P value	CSA vs. OSA P value
Age	60 (0.9)	58 (1.8)	56 (1.6)	0.03	0.37	0.40
Male	69% (3%)	75% (5%)	38% (5%)	0.0001	0.0001	0.30
Ischemic	62% (3%)	64% (6%)	44% (5%)	0.003	0.01	0.82
Dilated	23% (3%)	14% (4%)	35% (5%)	0.02	0.001	0.11
Others	15% (2%)	22% (5%)	21% (4%)	0.22	0.80	0.16
LVEF	34 (1.2)	27 (1.7)	38 (1.8)	0.06	0.0001	0.0008
BMI	33 (0.6)	29 (0.9)	31 (0.8)	0.03	0.12	0.0001
LVEDD	57 (1.1)	63 (1.6)	54 (1.2)	0.14	0.0001	0.0037
BNP	746 (66)	1341 (161)	873 (130)	0.35	0.02	0.001
A-fib	39% (3%)	32% (6%)	28% (5%)	0.06	0.57	0.31

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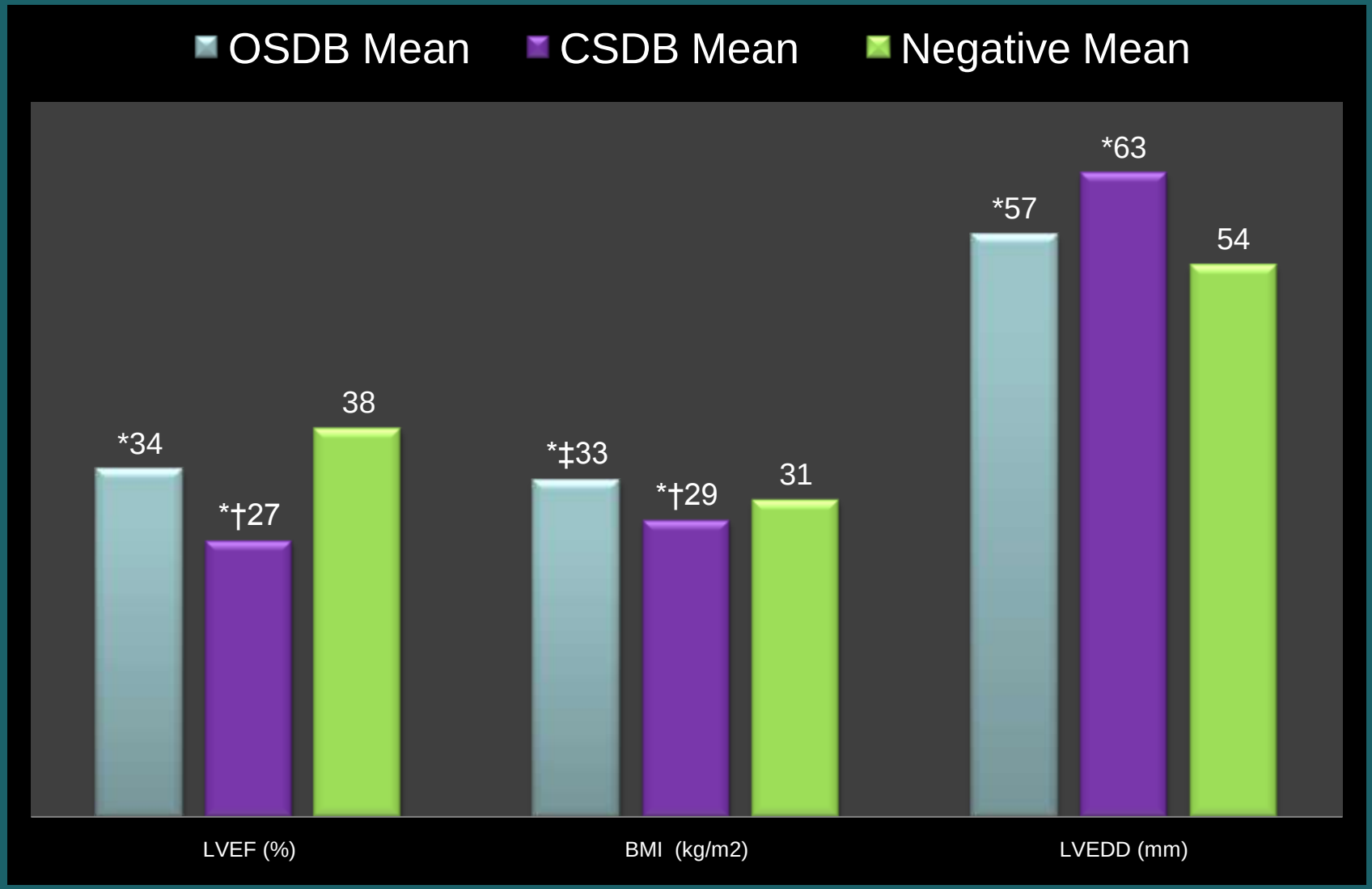
Predictors of SDB in all patients with ADHF

Variable Names	Pearson Correlation Coefficients	Number of Patients	95% Confidence Limits
AHI with EF	-0.10	370	(-0.20, 0.00)
AHI with LVEDD	0.19	281	(0.07, 0.30)
AHI with BMI	0.17	393	(0.07, 0.26)
AHI with A-Fib	-0.02	394	(-0.12, 0.08)
AHI with Age	0.02	395	(-0.08, 0.12)
AHI with BNP	0.004	294	(-0.11, 0.12)

Predictors of AHI in all patients with ADHF and SDB

Variable Names	Pearson Correlation Coefficients	Number of Patients	95% Confidence Limits
AHI with EF	-0.01	279	(-0.13, 0.11)
AHI with LVEDD	0.15	212	(0.01, 0.28)
AHI with BMI	0.18	298	(0.07, 0.29)
AHI with Age	-0.06	298	(-0.17, 0.05)
AHI with BNP	-0.006	231	(-0.13, 0.12)



‡ indicates a significant difference negative vs. OSDB (p value < 0.05) ,
† indicates a significant difference negative vs. CSDB (p value < 0.05),
*** indicates a significant difference CSDB vs. OSDB (p value < 0.05)**

Persistence of OSDB and validation of the Inpatient Testing

Comparison of AHI between the in-hospital study and the polysomnography in the validated OSA and CSA patients

	PSG AHI	Inpatient AHI	Difference between PSG AHI and Inpatient AHI	95% CI for the Difference
	Mean (SE) (N)	Mean (SE) (N)		
OSA	41.7 (3.9) (62)	37.4 (2.5) (62)	4.3	-1.1, 9.6
CSA	36.4 (7.2) (12)	49.1(5.9) (12)	-12.7	-29.9, 4.5

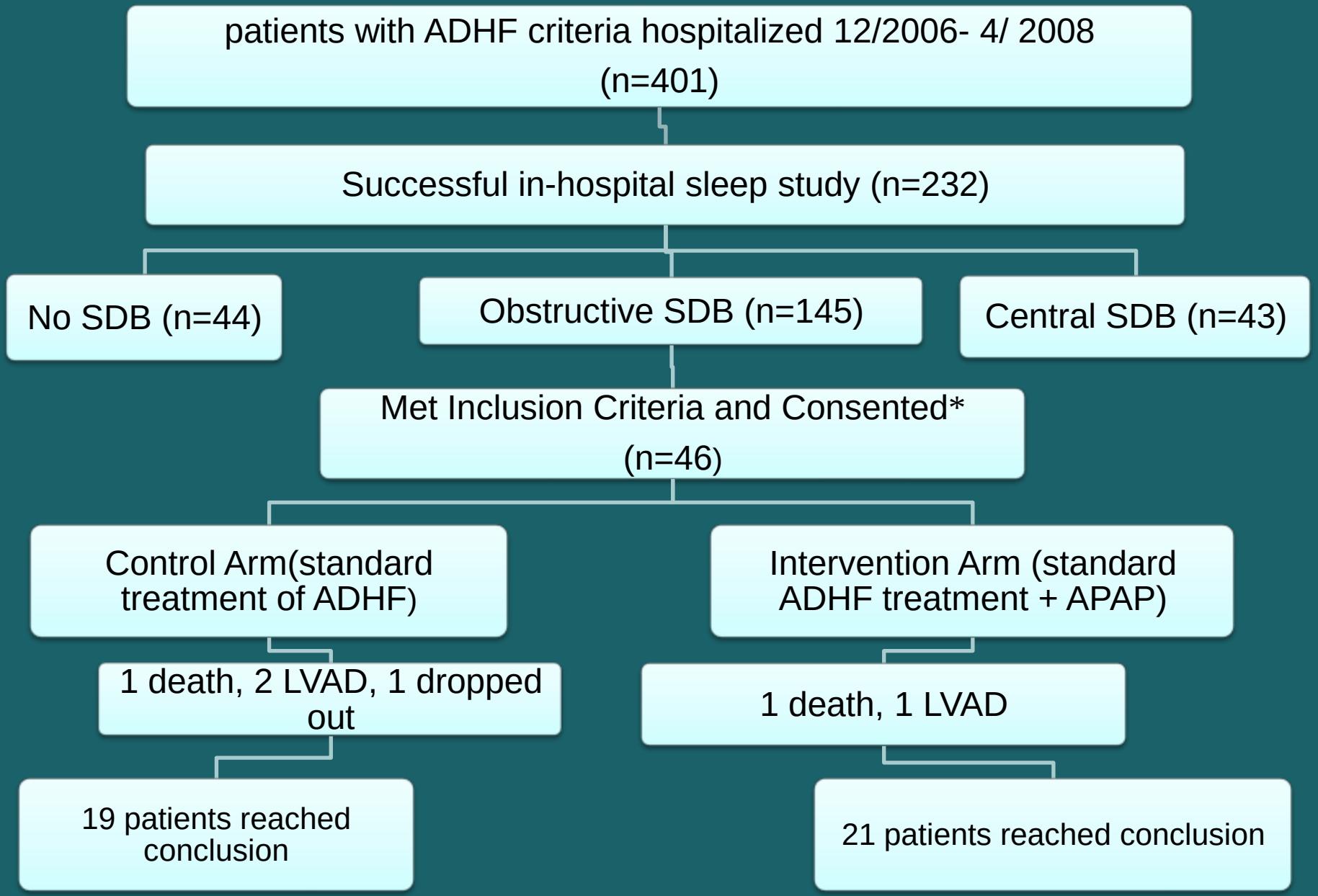
Khayat et al JCF-2009

Prevalence of SDB in Patients with ADHF

- SDB is present in 75% of patients
- OSA is more prevalent than CSA (57% vs. 18%)
- Increased LVEDD predicted having CSA
- Increased BMI predicted having OSA
- No other predictors of SDB and high prevalence support need for routine screening.

Role of OSA in the Acute Decompensation of heart Failure

- Hypothesis: Treatment of newly diagnosed OSA in patients with ADHF improves in-hospital and out-of-hospital outcomes.
  - Contractile function
  - Sympathetic activity
  - Hemodynamic measurements
  - Oxygenation
  - Functional Status

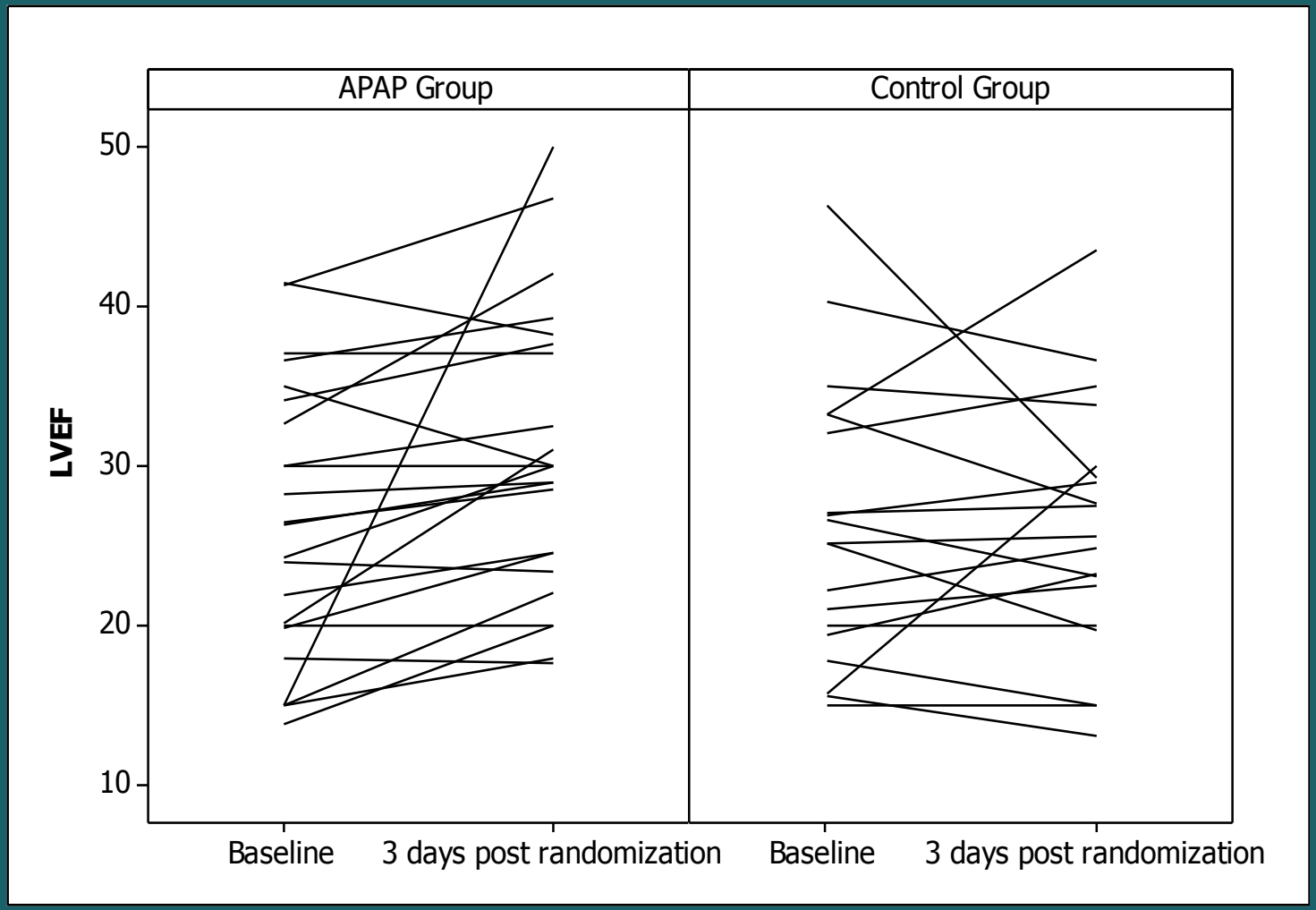


Khayat et al Chest 2009

Effect of In Hospital APAP on Cardiac Function three days post-randomization

	Control	Treatment	Difference (APAP Effects) (p-value)
LVEF			
three days post randomization	25.8	30.4	4.6
			(0.031)
change from base line (Final – Baseline)	-0.2	4.4	
LVESV			
three days post randomization	169	144	-24.8
			(0.0007)
change from base line (Final – Baseline)	3.2	-22.1	
LVEDV			
three days post randomization	228	204	-23.9
			(0.03)
change from base line (Final – Baseline)	2.1	-22	

Effect of In-hospital APAP on 3-Days LVEF



Khayat et al Chest 2009

Sensitivity Analysis of APAP Effect on LVEF in Patients with ADHF

Covariate Adjustments	APAP Effect		p-value
AHI	5.1		0.02
BMI	4.5		0.04
Cardiomyopathy Type	4.5		0.04
Gender	4.3		0.04
Interaction Effects with Median Split of Baseline Variable	APAP Effect for < Median	APAP Effect for > Median	Interaction Effect (difference between effects) p- value
LVEF	3.9	4.9	0.8
AHI	9.2	2	0.08
BMI	4.7	3.6	0.8
BNP	4.9	5.3	0.9
Categorical Variable			
Cardiomyopathy Type	Ischemic	Non- Ischemic	
	4.1	6.4	0.7

Khayat et al Chest 2009

Effect of PAP on hemodynamic and neurohumoral measures

Change from baseline	Control	Treatment	Difference (p-value)
Urinary Norepinephrine	-0.003	-0.011	-0.0008 (0.18)
BNP	17	-457	-474 (0.13)
BUN	-2.4	1.6	4.1 (0.18)
Creatinine	-0.03	0.21	-0.24 (0.19)
Systolic BP	-5.2	-6.5	-1.3 (0.78)
Diastolic BP	-1.2	-3	-1.9 (0.6)
Weight	-0.5	-2	-1.5 (0.048)

Khayat et al Chest 2009

Inpatient Treatment of OSA during ADHF

- Safe
- Improved LVEF; effect on long term cardiac outcomes and adherence is currently under evaluation.
- Feasible in a high risk population
- Requires expertise and training
- Associated with “excellent” tolerance and adherence