CORSO TEORICO-PRATICO
LA SLEEP APNEA: FATTORE DI RISCHIO CARDIOVASCOLARE
Bologna-16 GENNAIO 2020

Fibrillazione atriale e apnee notturne

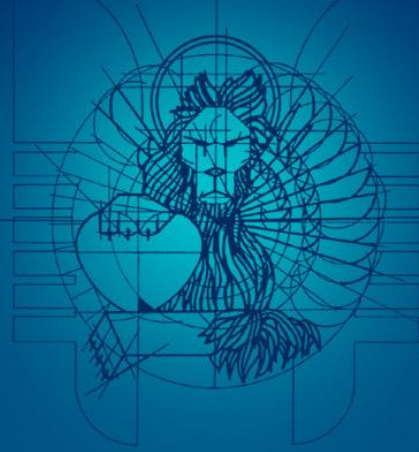
Dr. Paolo China

UOSD Elettrofisiologia ed Elettrostimolazione

Ospedale dell'Angelo- Mestre Venezia

Dipartimento Cardio-Toraco-Vascolare, Ospedale dell'Angelo, Mestre-Venezia

Agenda



- Association between SA and AF
- Possible pathophysiologic mechanisms
- AF causing SA
- Stroke, AF and SA
- Clinical implications

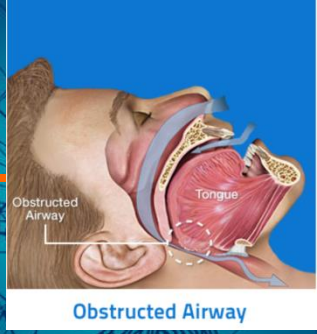
Sleep apnea: Obstructive and central

Sleep-disordered breathing (SDB)

- Obstructive sleep apnea (OSA)
- Upper-airway resistance syndrome

- Central sleep apnea
- Cheyne–Stokes respiration

Obstructive sleep apnea (OSA)



"Intermittent episodes of partial or complete obstruction of the upper airway during sleep, which disrupts normal ventilation and sleep architecture and is typically associated with snoring and daytime sleepiness"

Diagn: Apnea–hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) >5 and symptoms of excessive daytime sleepiness based on polysomnographic examinations

- Affects 5-56% of middle-aged men in western countries
- Affects over 15 million people: approximately 20% adults diagnosed with mild OSA and 7% adults with moderate- to-severe OSA
- Estimated 65–165 billion dollars is used in treatment of moderate- to-severe OSA

Young T. N Engl J Med 1993; 328:1 230-5. Todd K et al. Nat Sci Sleep 2010;2:39-45. Lopez-Jimenez F. Chest 2008;133:793-804 . Punjabi NM. Proc Am Thorac Soc 2008; 5: 136-43

Arrhythmia in patient with sleep apnea syndrome

Cardiac Arrhythmia and Conduction Disturbances During Sleep in 400 Patients With Sleep Apnea Syndrome

CHRISTIAN GUILLEMINAULT, MD, STUART J. CONNOLLY, MD, and
ROGER A. WINKLE, MD

This report presents the first study of cardiac arrhythmias and conduction disturbance in a large group (400 patients) with sleep apnea syndrome studied between 1974 and 1979 with 24-hour Holter electrocardiography and a simultaneously recorded polygraph during late afternoon or nocturnal sleep. Of the 400, 193 patients (48%) had cardiac arrhythmias during the recorded night. The mean number of apneic events, age, weight and lowest oxygen saturation during sleep were not significantly different in those with arrhythmias.

The most significant abnormalities were unsustained ventricular tachycardia in 8 patients, sinus arrest that lasted for 2.5 to 13 seconds in 43 patients, and second-degree atrioventricular conduction block in 31. Seventy-five had frequent (>2 beats/min) premature ventricular contractions during sleep. Fifty patients with significant arrhythmias had a tracheostomy and were monitored again after surgery. No arrhythmia was present in these patients except for premature ventricular contractions.

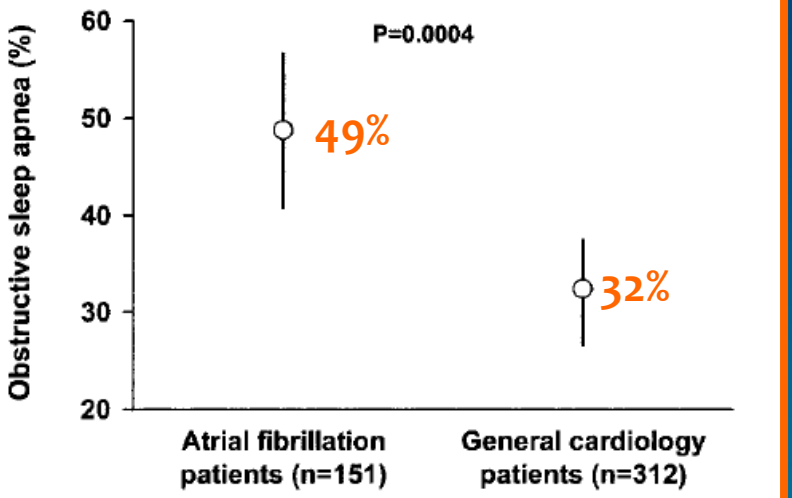
(Am J Cardiol 1983;52:490–494)

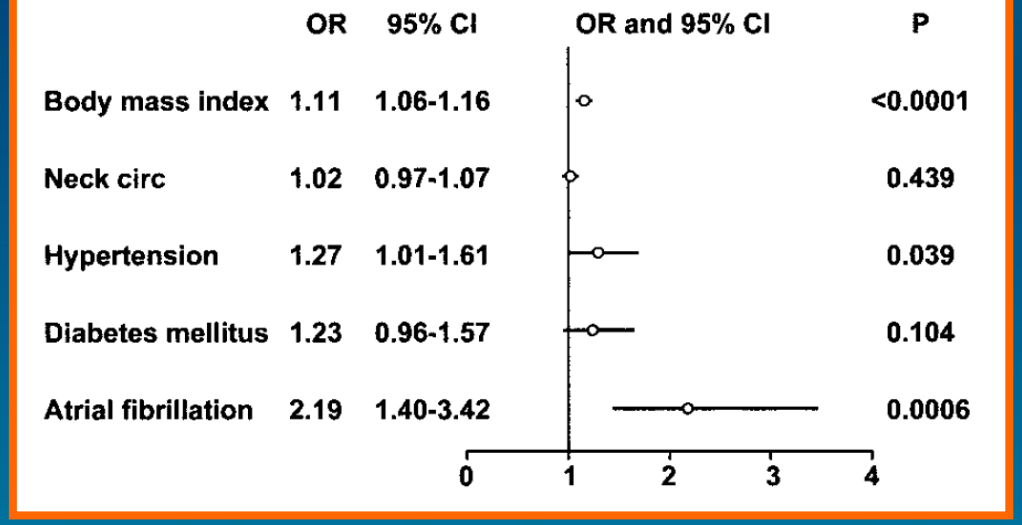
Cardiac arrhythmias during sleep in association with sleep apnea syndrome

Arrhythmia or Conduction Abnormality	Percent of Total Population	Patients (n)
Sinus arrest (2.5 to 13 s)	11	43
Second-degree atrioventricular cardiac block		
Mobitz type I	5	19
Mobitz type II	3	12
Ventricular tachycardia	3	12
Atrial tachycardia	7	28
Sinus bradycardia (<30 beats/min for at least 10 s)	7	29
Paroxysmal atrial fibrillation	3	10
Paroxysmal atrial flutter	1	3
Frequent premature ventricular contractions (>2/min)	20	75*

Guilleminault C. Am J Cardiol 1983; 52: 490-4

Association of Atrial Fibrillation and Obstructive Sleep Apnea





Among patients with AF, Obstructive Sleep Apnea is more prevalent than the general population (Berlin questionnaire)

Gami AS Circulation. 2004; 110:364-367

AF and OSA

(observational study review: 1983-2012)

Prevalence of OSA among patients with AF is estimated to be about 50% (11%–74%)

GUILLEMINAULT [1983]	400 OSA pts		**3% prevalence of nocturnal paroxymal AF** 1% paroximal A flutter 7% Atrial Tachycardia		
MOOE [1996]	121 pts Coronary artery bypass surgery		**AF incidence postoperatively** 32% for AHI >= 5 vs 18% for AHI <5 39% for ODI >= 5 vs 18% for ODI <5		Oxygen Desaturation Index independent predictor of post-operative AF onset
JAVAHERI [1998]	81 pts males, HF (LVEF < 45%)	11% prevalence of OSA	**22% prevalence of AF in pts with SDB** with a (4) four-fold increase in relative risk		
GAMI [2004]	151 Pts Electroversion for AF 312 Controls (no AF)	49% prevalence of OSA in patients with AF	**OR 2.19** for risk of AF in OSA patients		
PORTHAN [2004]	59 Pts with AF 56 Controls without AF	32% prevalence of OSA in patients with AF			Neck circumference independently associated with AF in males
MEHRA [2006]	228 Pts with SDB (RDI >= 30) 338 Controls w/o SDB (RDI < 5)		**4.8% versus 0.9% prevalence of AF** **OR 4.02** for AF after adjusting for age, sex, body mass index, CAD		
GAMI [2007]	3542 Obese subjects	74% prevalence of OSA (for AHI >5 events/h)	**Incidence of AF at 5-year follow-up:** 4.3% in patients with OSA, 2.1% in patients without OSA **HR 2.18 for AF in patients with OSA**		
PEDROSA [2010]	80 pts Hypertrophic cardiomyopathy	40% prevalence of OSA	31% prevalence of AF in OSA patients 6% prevalence of AF in pts without OSA		OSA and left atrial diameter are independently associated with AF
PATEL [2010]	3000 pts with PVAI for AF	21.3% prevalence of OSA	27% incidence of AF recurrence after treatment in OSA pts		OSA independently associated with failure of PVAI
MATIELLO [2010]	174 pts Circumferential pulmonary vein ablation for AF	24.2% prevalence of OSA	**Incidence of AF recurrence after treatment:** 51.5% for AHI < 10 85.7% for AHI >= 30		
ABE [2010]	1350 pts with OSA (44 no SBD)		**Prevalence paroxysmal AF during polysomnography:** 1% for AHI 5–15 3.3% for AHI 15–30 3.4% for AHI >30	**Prevalence chronic AF:** 2.3% for AHI < 5 3.6% for AHI 5–15 5.2% for AHI 15–30 3.8% for AHI > 30	**Prevalence paroxysmal AF:** 2.3% for AHI < 5 7.6% for AHI 5–15 5.2% for AHI 15–30 6.6% for AHI > 30
BITTER [2012]	82 Pts undergoing PV vein ablation for AF	20% prevalence of moderate to severe OSA	**AF recurrence after PV ablation** 45.5% for moderate to severe SDB 24.5% for mild or no SDB		

Rossi VA et al. Eur Respir J 2013; 41: 1439-1451

Prevalence of AF in patients with OSA

Sleep Heart Health Study

- Prospective longitudinal cohort in 6,400 participants
- Aimed to assess arrhythmia prevalence in patients with SA
- All patients underwent sleep testing
- 228 individuals with severe SA were compared to 338 individuals without OSA

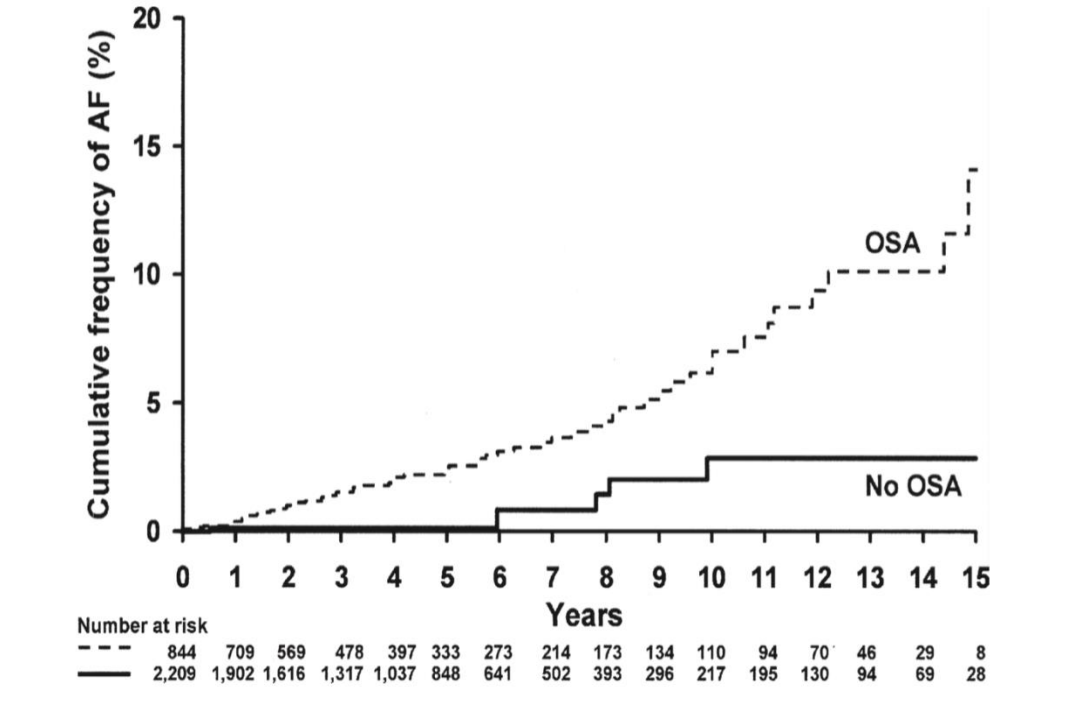
- Patients with OSA had 4.8% prevalence of AF
- OSA ~5 fold increased risk of AF
- Adjusted risk (Age, BMI, CAD) of 4.02 [1.03–15.74]; 95%CI

Am J Respir Crit Care Med 2006

Incidence of AF in patients with OSA

Olmsted County sleep study registry

- 3542 individuals without AF at baseline followed longitudinally, 5 Y
  1) 4.3% in pt with OSA
  2) OSA is independent predictor for new AF: HR 2.18



Greater OSA severity conferred proportionally higher AF risk:

1.31 / AHI unit

Gami et al. J Am Coll Cardiol 2007;49:565-571

Sleep apnea and AF

Is the relationship between sleep apnea and AF an

association/shared risk factors

or is it truly

causative/indipendent risk factor?

OSA and AF share multiple risk factors

- Advanced age
- Male gender (2:1)
- Obesity
- Hypertension
- Heart failure

Nalliah et al . J Cardiovasc Electrophysiol, 2016; 27: 1001-10

Sleep apnea and AF

Epidemiological data suggest that

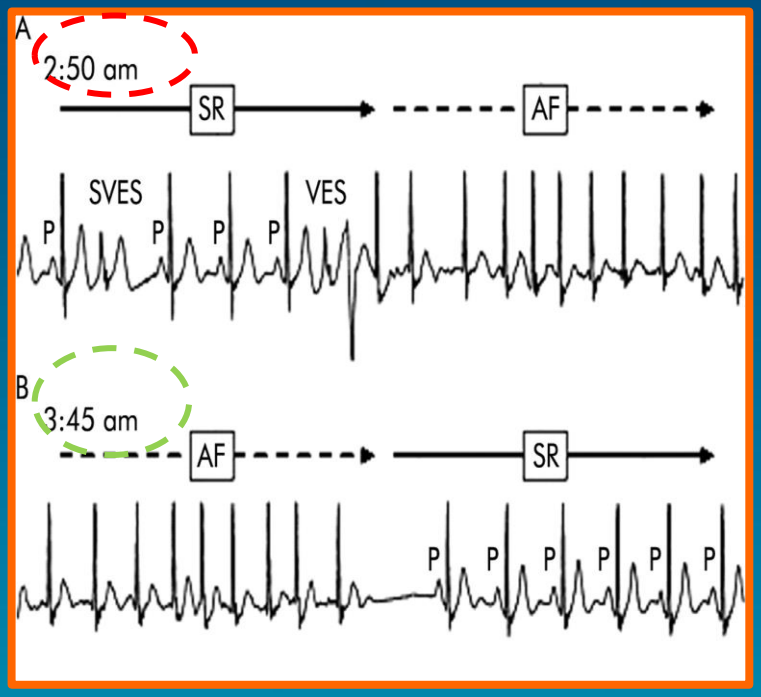
1) OSA independent of obesity is associated with AF
2) Obesity independent of OSA is associated with AF, particularly in younger individuals *
3) The weight loss in obese individuals ° or primary treatment of OSA § can reduce the burden of AF

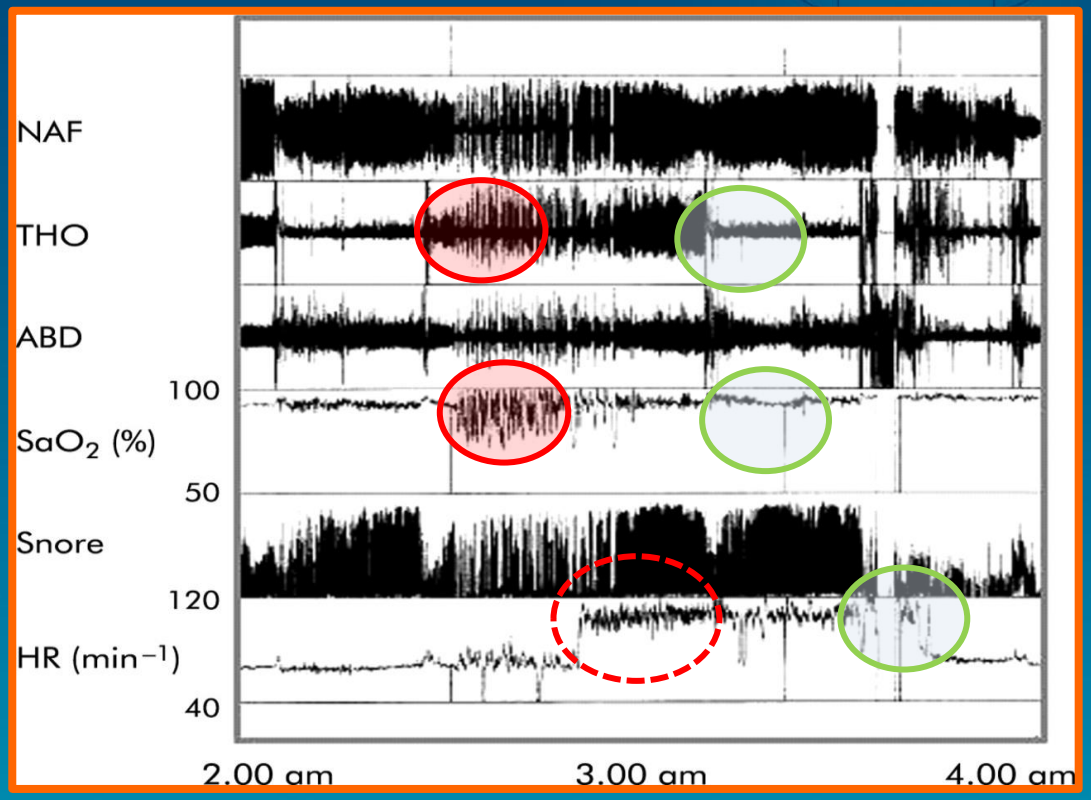
Thus, the link between OSA and AF seems more than an association

* Gami AS. J Am Coll Cardiol. 2007;49:565–71
° Abed HS JAMA. 2013;310:2050–60
§ Kanagala R, Circulation. 2003;107:2589–94

Nocturnal AF and obstructive sleep apnea

The onset of AF was preceded by a long apnoeic event (48 s) with marked oxygen desaturation (SaO2 67%)





After a period without apneas, spontaneous reversal to sinus rhythm occurred

Polysomnographic trace

Schulz R et al. Thorax 2005;60:174

Triggering of nocturnal arrhythmias by

Table 4

Risk of arrhythmia following a respiratory disturbance compared to the risk of arrhythmia during normal nocturnal breathing

	Number of arrhythmias included in each analysis	Odds Ratio (95% CI)
Primary Overall Analysis	**62**	**17.5 (5.3–58.4)**
Sub-Analyses		
By Arrhythmia type		
PAF	15	17.9 (2.2–144.2)
NSVT	47	17.4 (4.0–75.7)
By Sleep stage		
NREM	42	14.2 (4.2–48.0)
REM	20	*
By Respiratory disturbance subtype		
No respiratory disturbance	18	-reference-
Respiratory disturbance without hypoxia (nadir $SpO_2 \leq 92\%$) or arousal	14	24.1 (5.4–106.6)
Respiratory disturbance with hypoxia	20	13.6 (3.7–50.6)
Respiratory disturbance with arousal	10	21.8 (4.5–106.3)

18-fold increase in the relative risk of nocturnal arrhythmia within 90 seconds (a physiologically-defined interval) following a respiratory disturbance in individuals with a broad range of SDB severity

Monahan KJ Am Coll Cardiol. 2009;54:1797–804

Triggering of nocturnal arrhythmias by sleep-disordered breathing events: TEMPORAL RELATIONSHIP

First studies focused among subjects with severe SDB (AHI ≥ 30 events/hour) compared to those with an AHI < 5 events/hour*

IF we INCLUDED all records with an AHI < 30 events/hour

The majority of identified arrhythmias occurred among those with only moderate levels of SDB (AHI 5–30 events/hour)

- In this cohort most of the respiratory disturbances preceding arrhythmias were hypopneas (as opposed to apneas)
- Neither the severity of SDB nor the severity of individual respiratory disturbances needs to be extreme in order to increase the risk of arrhythmia

*Mehra R et al Am J Respir Crit Care Med 2006;173:910–916

° Monahan KJ Am Coll Cardiol. 2009;54:1797–804

Mechanistic Relationship

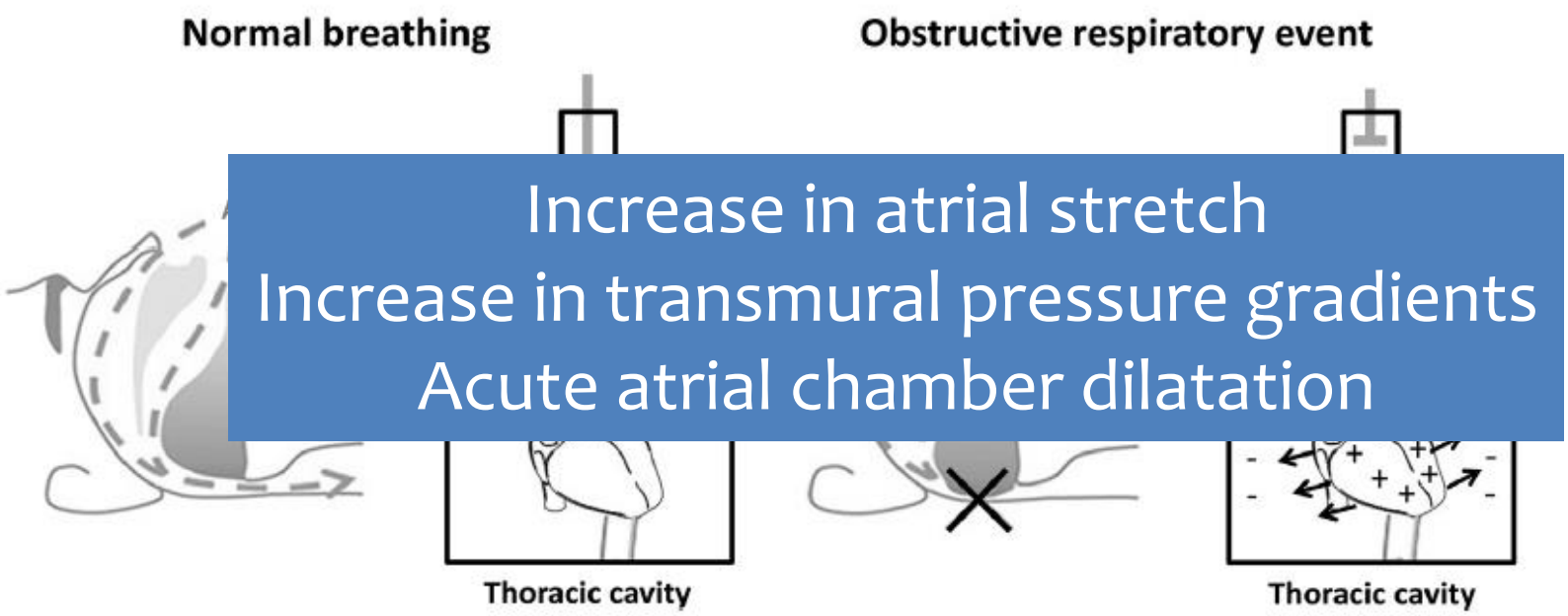
1. Negative intra-thoracic pressure
2. Autonomic imbalance
3. Hypoxia

Acute effects

4. Structural remodeling

Chronic effects

Mechanical Effects of NTP on Heart Function: focus on atria



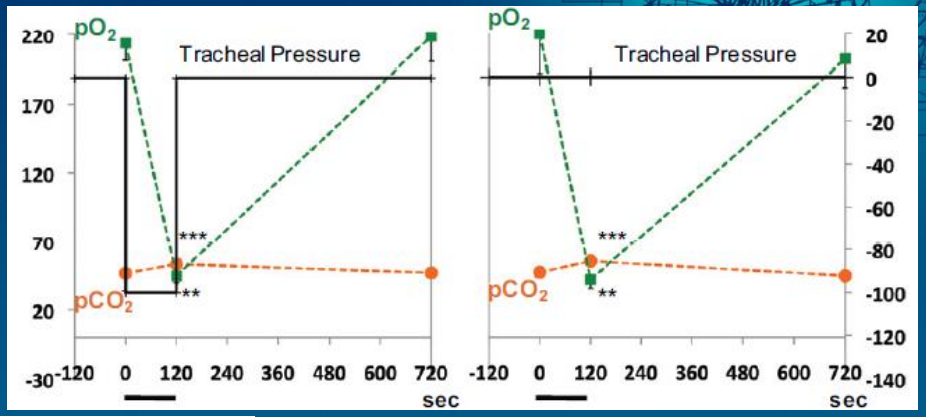
Increase in atrial stretch
Increase in transmural pressure gradients
Acute atrial chamber dilatation

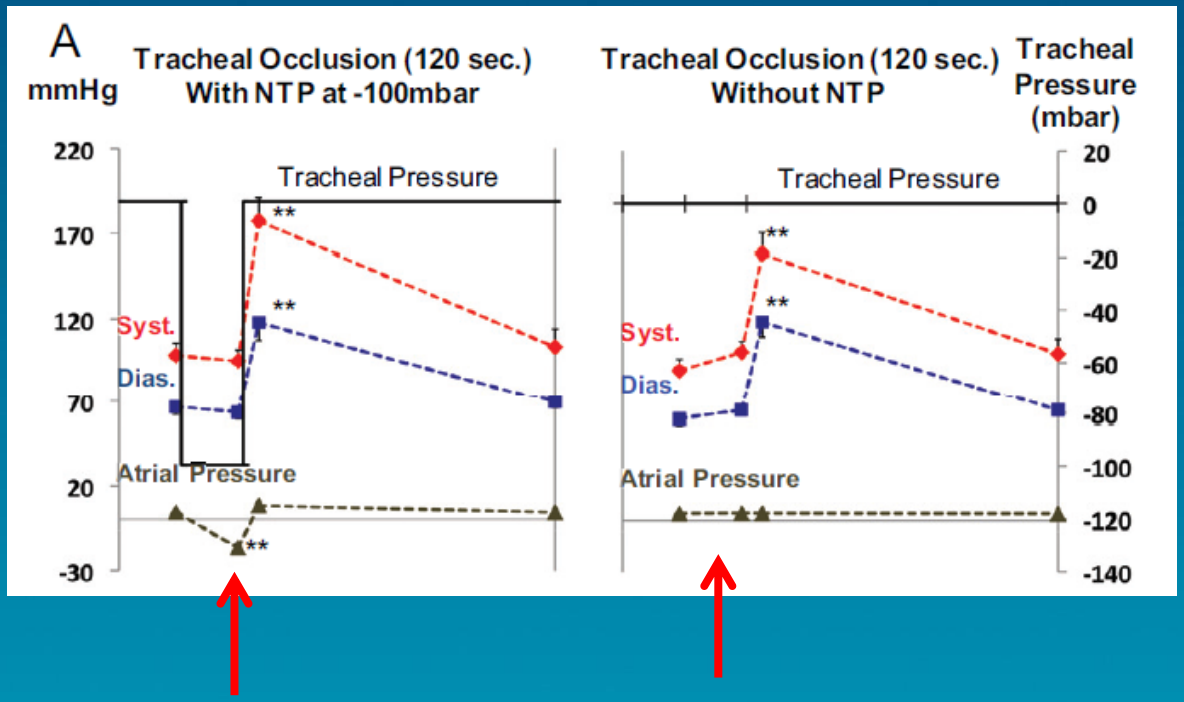
Application of negative tracheal pressure at -80 mbar resulted in a negative right atrial pressure of -16 mbar

Linz D. et al – Sleep medicine review 2015: 1-8

Hemodinamic effect: Negative Tracheal Pressure in OSA

- **Hemodynamic Parameters** (Blood pressure and Right Atrial Pressure)
- **Blood Gases**



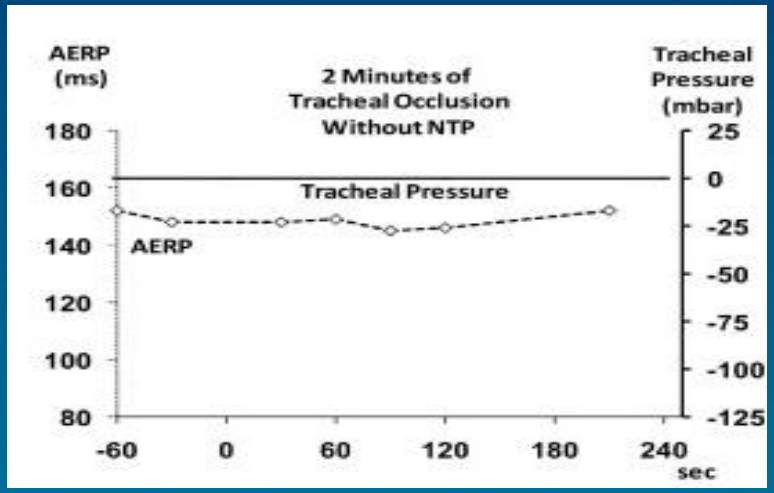


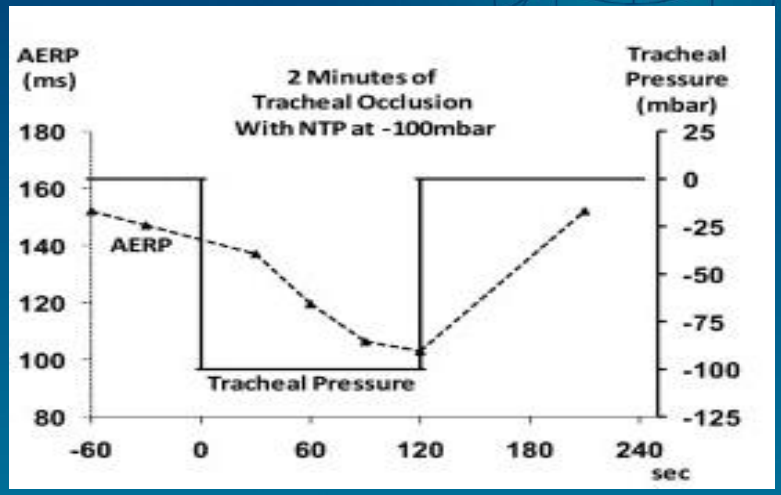
No significant change in BP
Righ Atrial pressure decrease

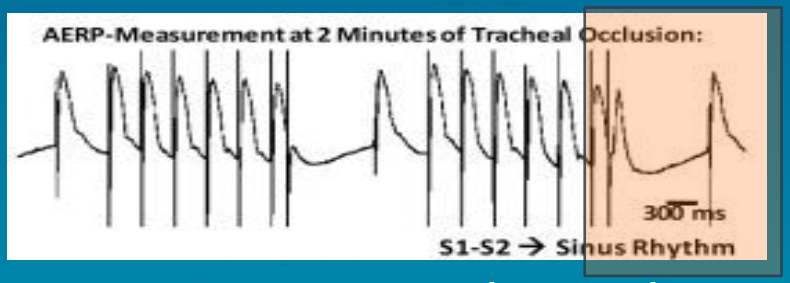
Linz D. et al – Heart Rhythm 2011; 8:1436-1443

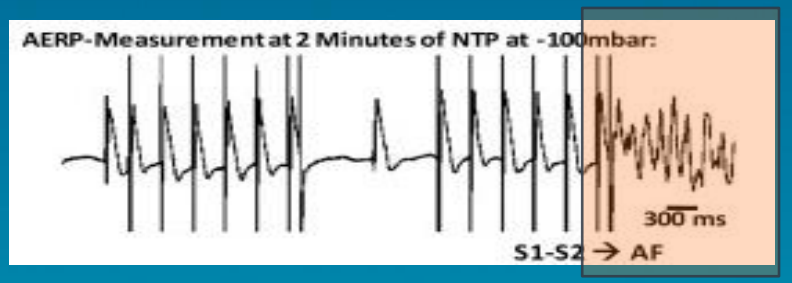
Electrical effect: Negative Tracheal Pressure in OSA

Negative Tracheal Pressure (NTP) during obstructive respiratory events promotes AF… ***by vagal activation***









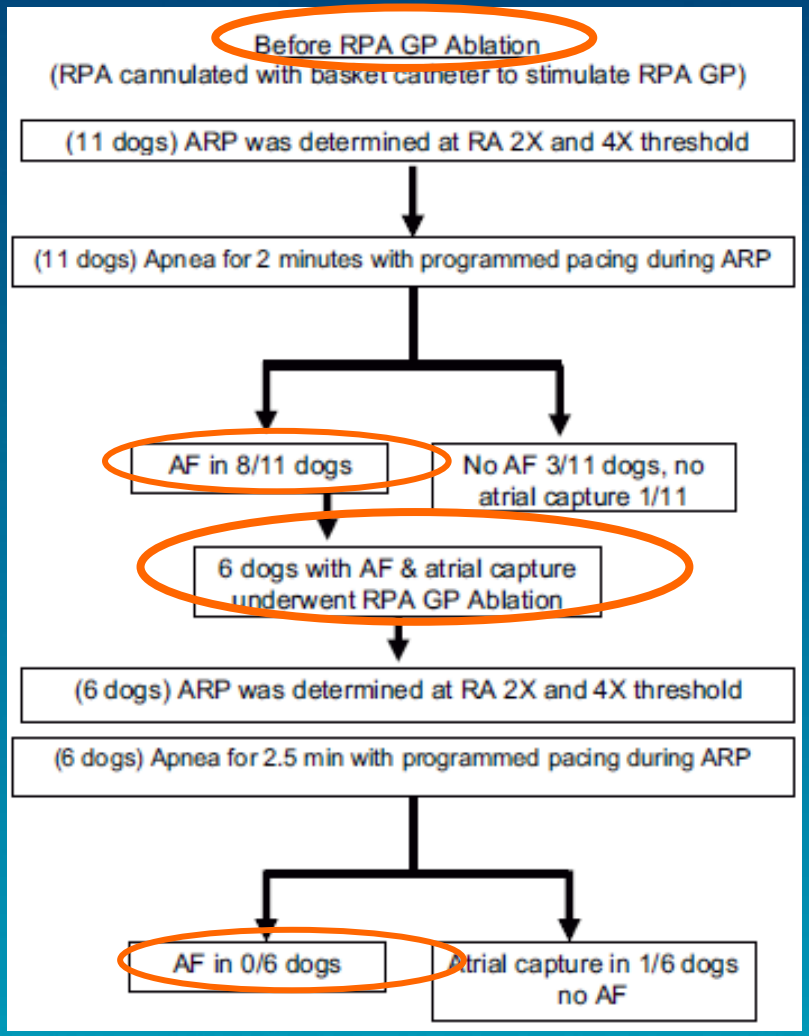
1)Progressive AERP and MAP duration shortening associated with increased AF inducibility

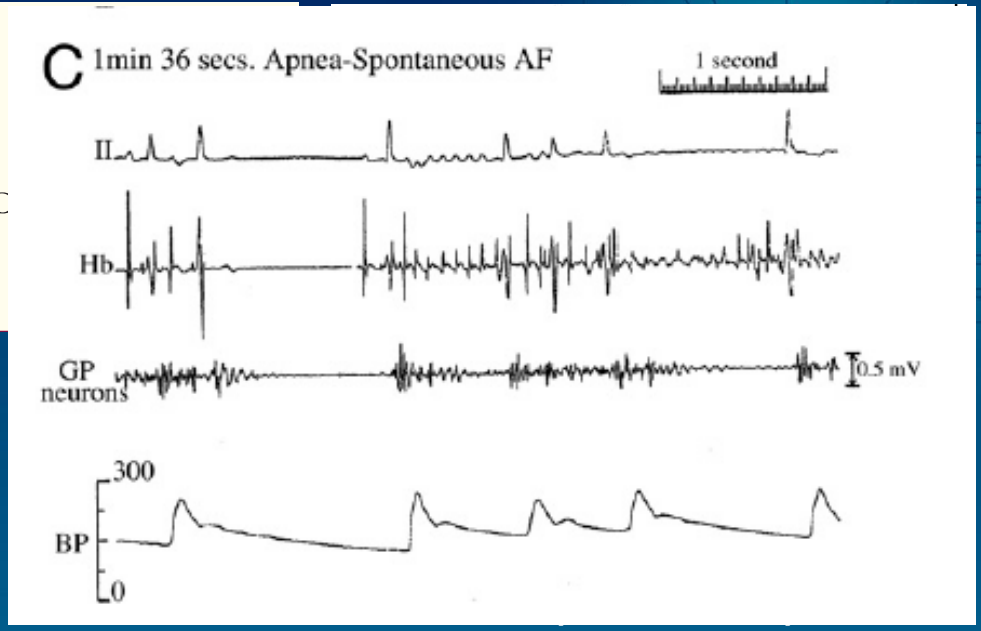
2) NTP-induced AERP shortening and AF inducibility were prevented by atropine or vagotomy

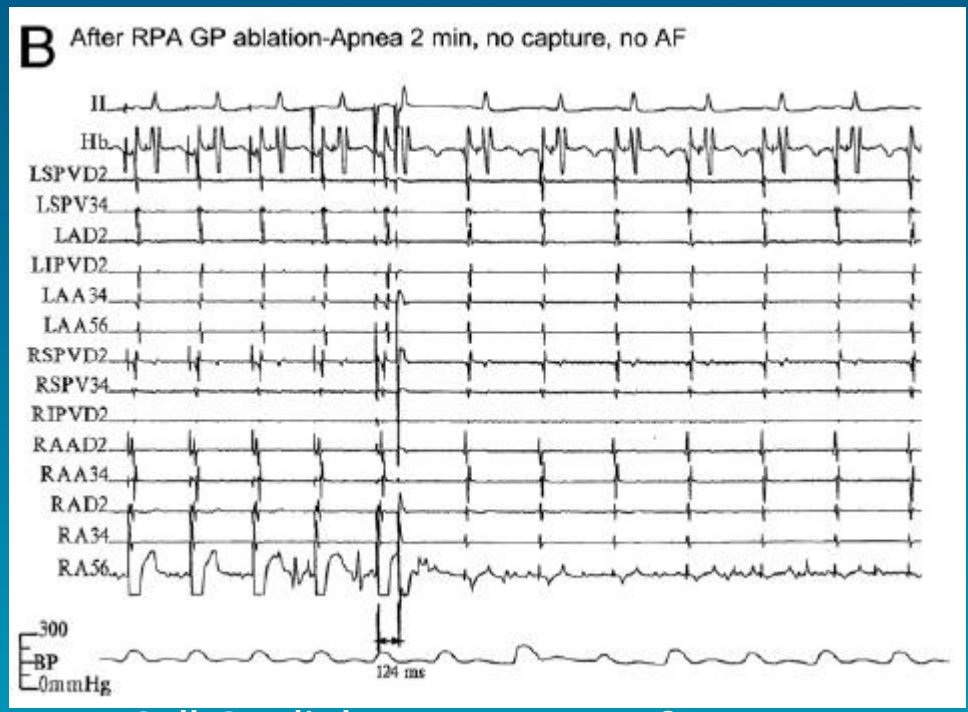
Linz D. et al – Heart Rhythm 2011; 8:1436-1443

The Role of Ganglionated Plexi in Apnea-Related Atrial Fibrillation

Muhammad Ghias, MD, Benjamin J. Scherlag, PHD, Zhibing Lu, MD
Annerie Moers, MD, Warren M. Jackman, MD, Ralph Lazzara, MD,
Oklahoma City, Oklahoma





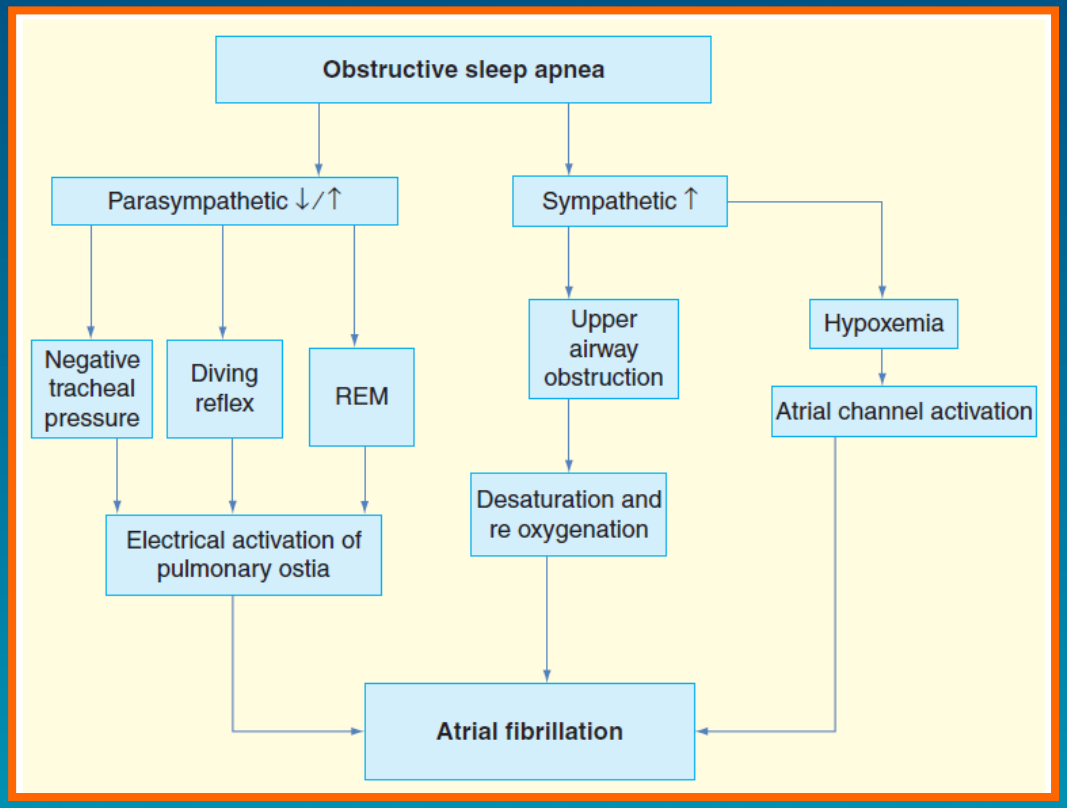


J Am Coll Cardiol 2009;54:2075–83

OSA, AF and dysautonomia

1) *increased sympathetic activation* during apneic episodes in OSA

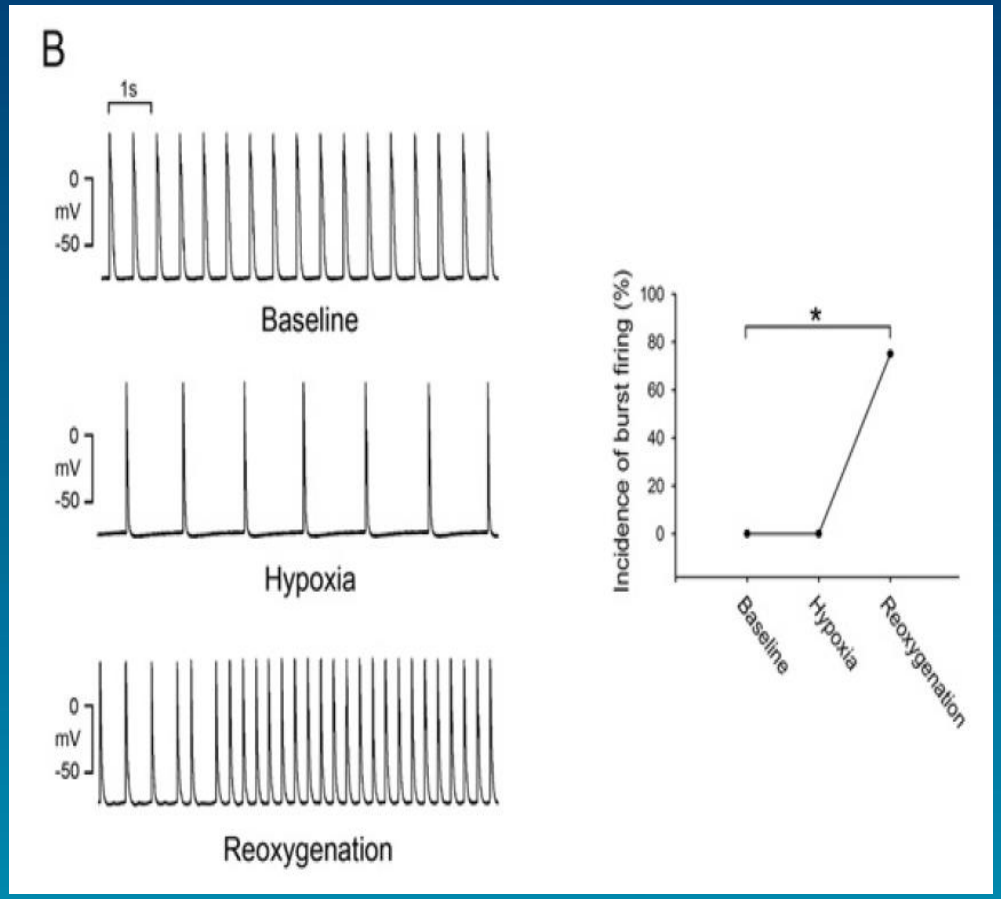
2) simultaneous *sympathetic and parasympathetic activation* (sympatho-vagal imbalance) =>Severe bradycardia and atrioventricular conduction disturbances together with the arousal reaction characterized by activation of the sympathetic system and postapneic blood pressure rises



Oza NM et al. Expert Rev Cardiovasc Ther 2014; 12: 613-621

Hypoxemia, hypercapnia and acidosis are invariably linked with OSA

Hypoxemia > Role than Hypercapnia



hypoxia caused:

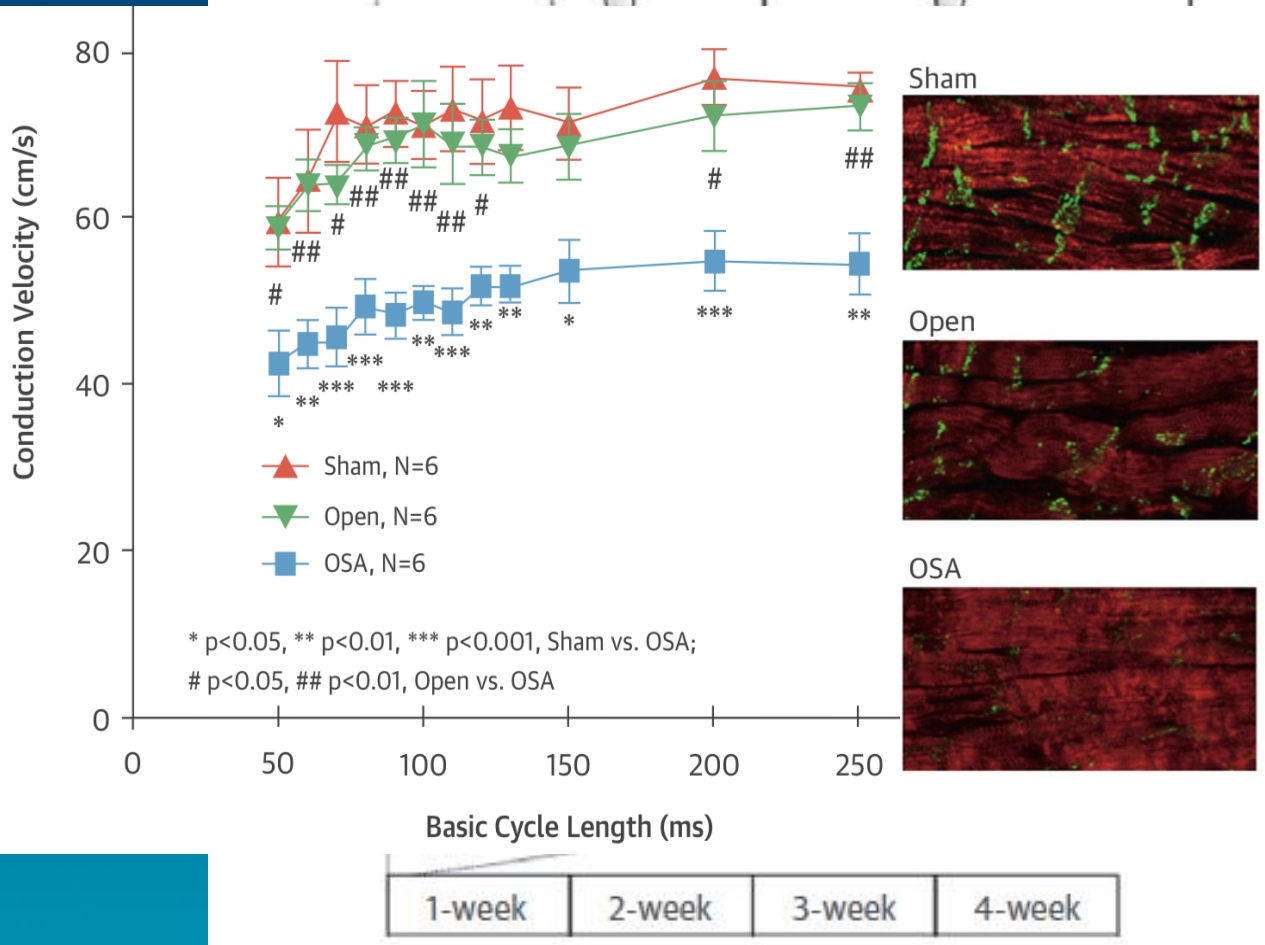
1) depressed conduction velocity and a marked increase in inhomogeneity in conduction both leading to increased vulnerability ofthe atrium for reentrant arrhythmias

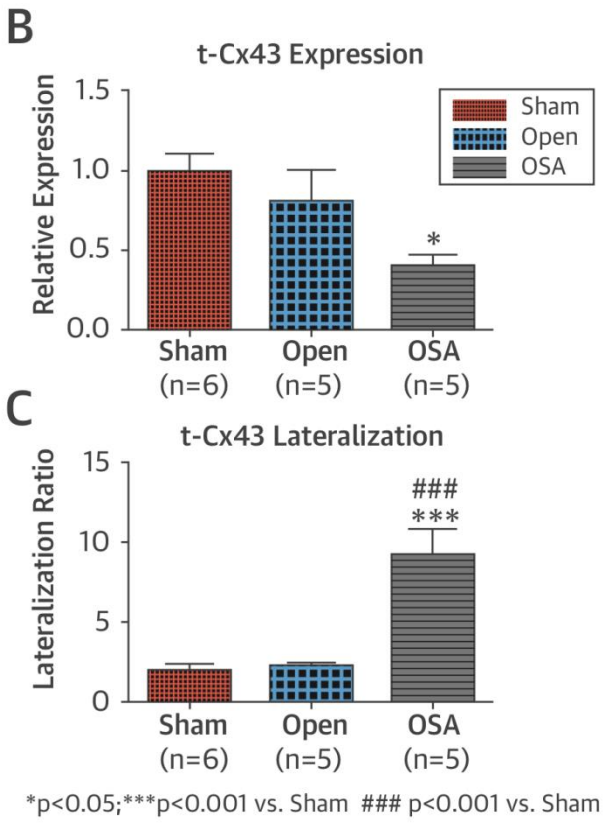
2) hypoxia followed by reoxygenation induced pulmonary vein burst firing

However in a pig model some changes in blood gases alone were insufficient to promote AF

Lin YK Clin Sci (Lond) 2012;122:121e32

Chronic effects mediated by remodeling of the atria

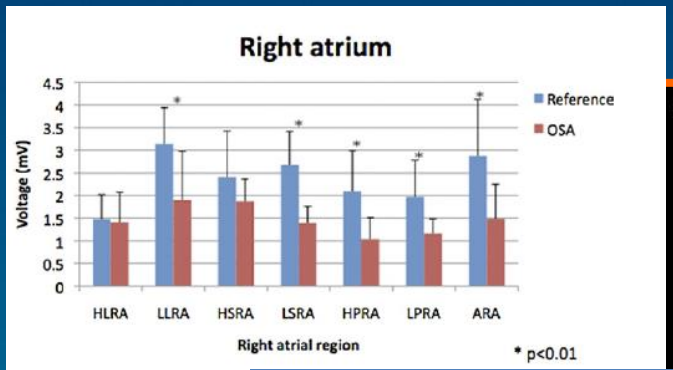


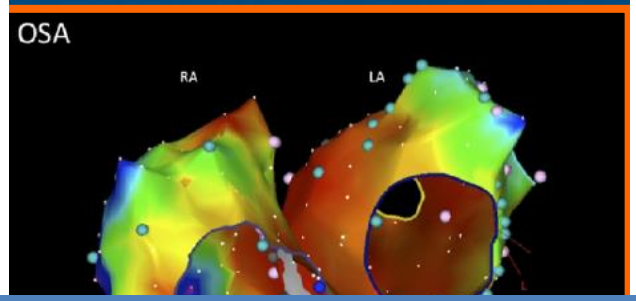


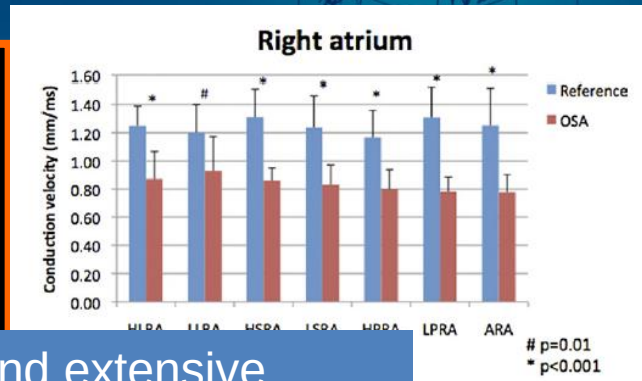
Iwasaki Yu-Ki, JACC 2014, 19-14

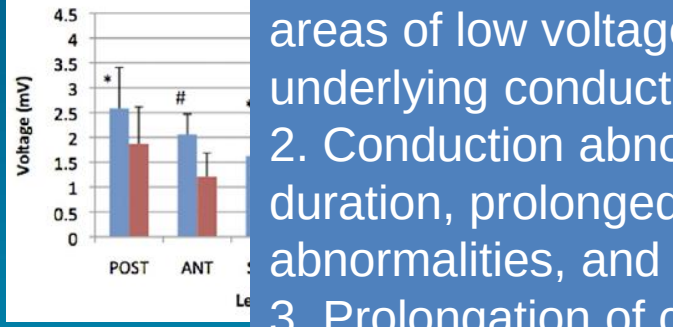
Atrial remodeling in OSA pts

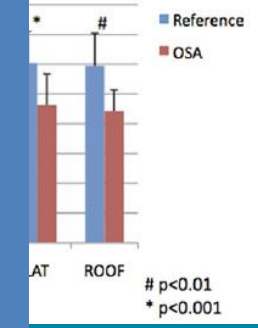
20 Pts with OSA vs 20 without OSA, same RF



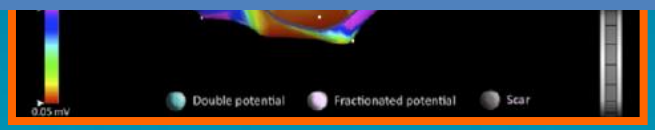








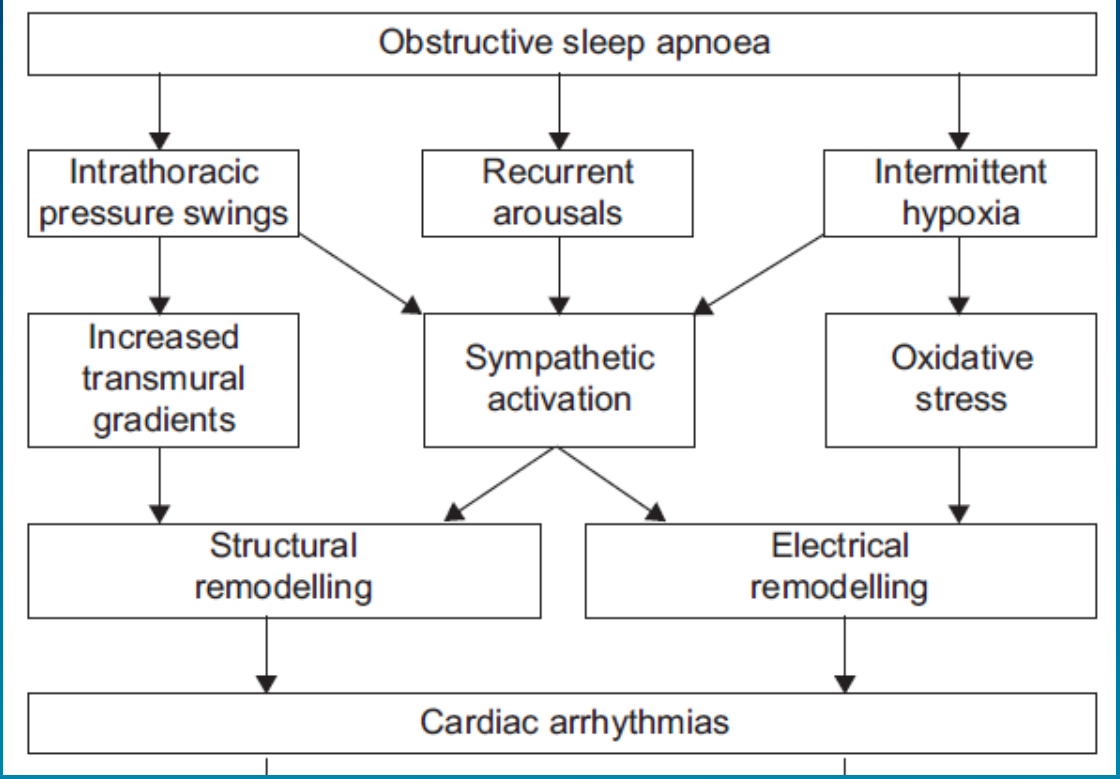
1. Structural change with increased atrial size and extensive areas of low voltage and regions of electrical silence (fibrosis, or underlying conduction dissociation)
2. Conduction abnormalities characterized by longer P-wave duration, prolonged conduction times, site-specific conduction abnormalities, and greater regions of atrial complex electrograms
3. Prolongation of correct sinus node recovery time, suggesting sinus node remodeling.
4. No difference in ERP in the resting state



Dimitri H et al. Heart Rhythm 2012; 9:321-327

Association between OSA and cardiac arrhythmias

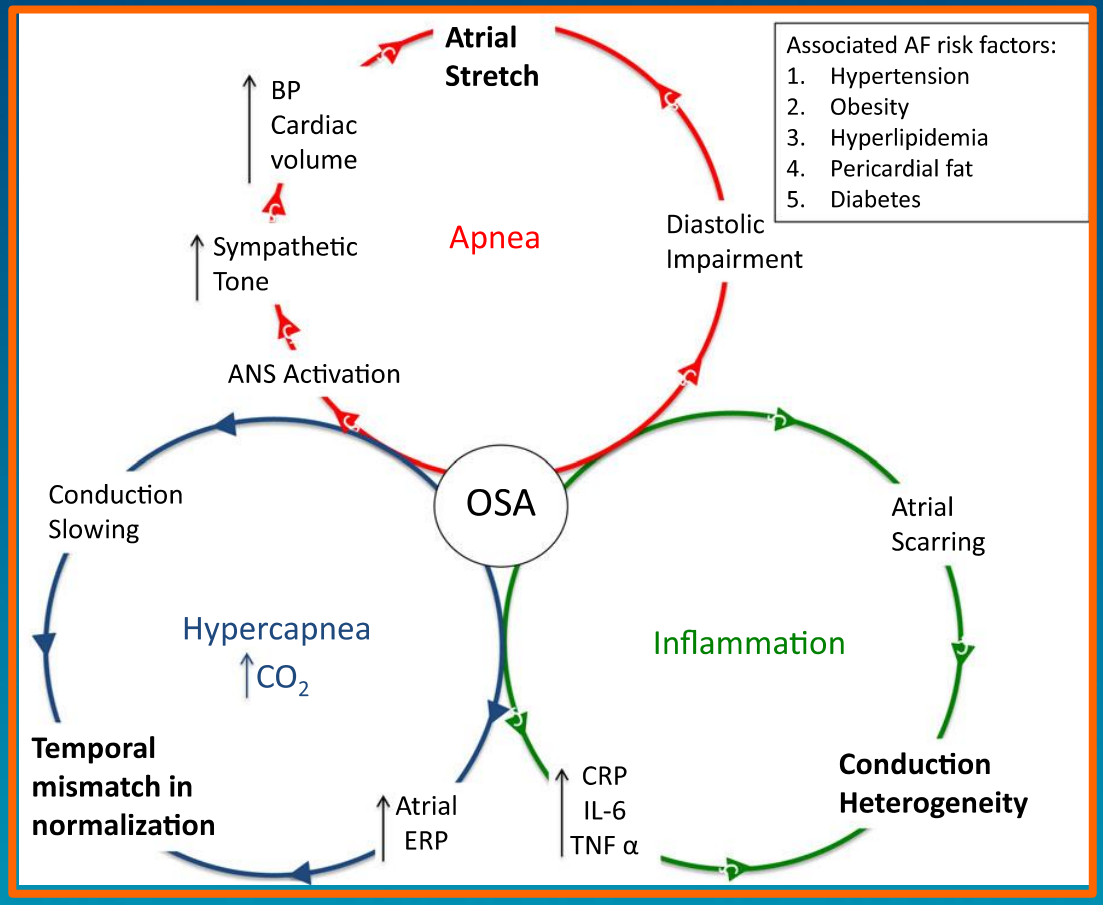
Possible mechanisms:



Rossi V.A. et al. - Eur Respir J 2013; 41: 1439-1451

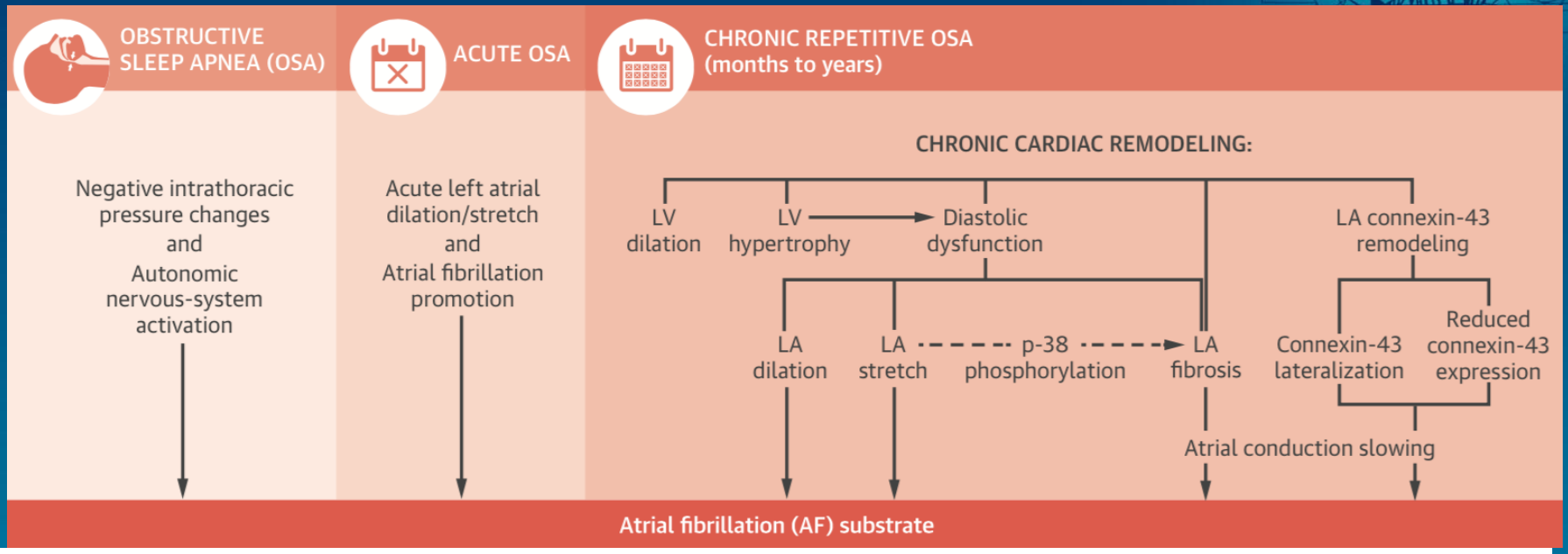
Association between OSA and cardiac arrhythmias

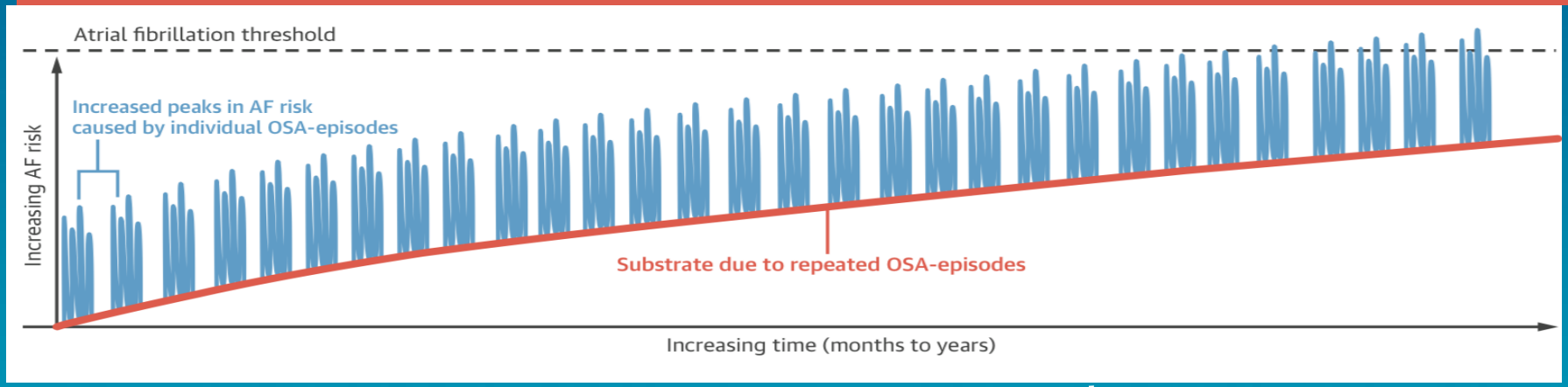
Possible mechanisms:



Nalliah et al . J Cardiovasc Electrophysiol, 2016; 27: 1001-10

AF related to OSA is *substrate based* rather than *trigger based*?





Iwasaki Yu-Ki, JACC 2014

Impact of OSA on outcomes in patients with AF

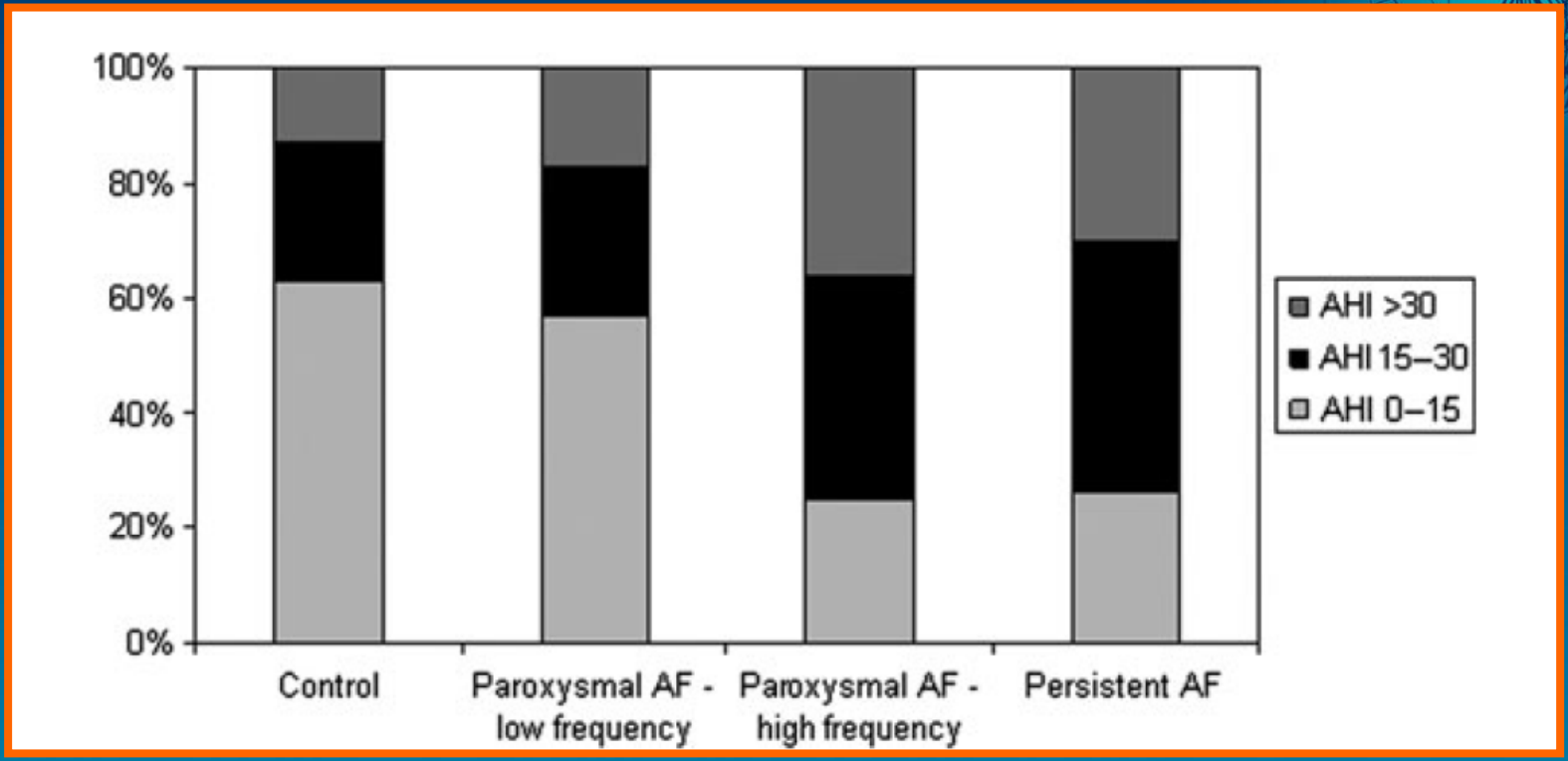
Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)

AF patients with OSA have worse symptoms

	Overall (N = 10,132)	No OSA (n = 8291)	OSA (n = 1841)	P
AF type				
First detected/new onset	4.7	5.0	3.7	.043
Paroxysmal	51	51	50	
Persistent	17	17	18	
Permanent	28	28	28	
Family history of AF	15	14	17	.0091
Duration of AF diagnosis, m	47 (17-93)	47 (17-94)	46 (18-91)	.92
Sinus rhythm on most recent ECG	33	33	34	.83
EHRA symptom level				
No symptoms	38	39	33	<.0001
Mild	45	45	45	
Severe	15	14	19	
Disabling	1.8	1.7	2.7	
$CHADS_2$ risk groups				
0	6.4	6.6	5.3	.73
1	22	22	23	
≥2	72	72	72	
CHA_2DS_2-VASc score (mean ± SD)	3.9 ± 1.8	4.0 ± 1.8	3.7 ± 1.8	<.0001
Prior treatment				
Oral anticoagulation therapy	82	81	85	<.0001
Antiarrhythmic drug	45	44	52	<.0001
Prior cardioversions	30	28	38	<.0001
Prior catheter ablation of AF	5.5	5.0	7.7	<.0001
Current treatment				
Oral anticoagulation therapy	76	75	79	.0020
Antiarrhythmic drug	29	28	33	<.0001
Rhythm strategy	32	31	35	.0037

Holmqvist et al. Am Heart J 2015;169:647-654

AF type in OSAS patients



High frequency paroxysmal AF and persistent AF are both associated with presence of OSA

Stevenson Eur Heart J 2008; 29: 1662-1669

Impact of OSA on outcomes in patients with AF

Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)

AF patients with OSA have higher risks of hospitalization but..
… similar mortality, major adverse cardiovascular outcome and AF progression

Table III. Association of OSA and 2-year outcomes

Outcome	OSA (n = 1763) No. of events (events/100 patient-years)	No OSA (n = 7879) No. of events (events/100 patient-years)	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
All-cause death	127 (1.45)	672 (5.35)	0.83 (0.68-1.01)	.057	0.94 (0.77-1.15)	.54
First hospitalization (all-cause)	866 (43.3)	3,324 (35.0)	1.17 (1.09-1.27)	<.0001	1.12 (1.03-1.22)	.0078
CV death, MI, stroke/TIA	106 (3.77)	494 (3.99)	0.96 (0.75-1.15)	.51	1.07 (0.85-1.34)	.57
Major bleeding	123 (4.47)	463 (3.79)	1.18 (0.96-1.44)	.12	1.18 (0.96-1.46)	.11

Outcome	OSA (n = 1223) No. of events (percent)	No OSA (n = 5349) No. of events (percent)	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Progression of AF type	221 (18)	984 (18)	1.05 (0.88-1.24)	.60	1.06 (0.89-1.28)	.51

AF progression occurred in 221 (18% in both groups)

Holmqvist et al. Am Heart J 2015;169:647-654

Central Sleep-disordered and AF

Central sleep apnea (CSA) is the cessation of breathing with no thoracoabdominal effort

Rarely found in the general population

CSA is characterized by breathing instability with highly sensitive chemoresponses and prolonged circulation time

Common sleep disordered breathing pattern seen in patients with chronic heart failure: prevalence of ***25-40%***

Both OSA and CSA are prevalent in patients with heart failure

May AM et al. Am J Respir Crit Care Med 2016; 193: 783-91

Central Sleep-disordered and AF

Complex pathways of medullary and aortic receptor chemosensitivity are at the root of the pathophysiology of CSA

There is often a relative state of ***hypocapnia*** at baseline

Hypoxia is unlikely to be playing a major role in triggering AF, since apnea-related hypoxia is less pronounced in CSA than in OSA

Unlike OSA, which is worse during REM sleep, Hunter-Cheyne-Stokes breathing in CSA is typically ***worse in NREM sleep***

May AM et al. Am J Respir Crit Care Med 2016; 193: 783-91

Association Between Atrial Fibrillation and Central Sleep Apnea

	Idiopathic CSA	OSA
Age, y	56.8 ± 15.8	56.6 ± 12.4
Men:women	51:9	51:9
Body mass index, kg/m^2	29.2 ± 4.5	30.0 ± 4.5
SaO_2 minimum, % [range]	88.1 [85.1, 90.6]	85.1 [79.5, 89.3]*
AHI, events/h		
Total	30.4 ± 17.7	30.3 ± 16.8
Central	23.1 ± 14.7	2.5 ± 3.5
Obstructive	7.2 ± 7.7	27.8 ± 16.5
Atrial fibrillation, no. (%)	16 (27)†	1 (1.7)
Hypertension, no. (%)	17 (28)	30 (50)*

60 consecutive patients with idiopathic central sleep apnea (apnea-hypopnea index > 10 events per hour, > 50% central events) VS 60 patients with obstructive sleep apnea

CSA has a higher prevalence of AF than OSA

Leung et al. SLEEP 2005;28(12): 1543-1546

Central Sleep-disordered Breathing Predicts Incident Atrial Fibrillation in Older Men

n= 843 of ambulatory older men without prevalent atrial fibrillation

Table 3. Age-stratified Adjusted Associations of Sleep-disordered Breathing Predictors and Incident Atrial Fibrillation or Flutter

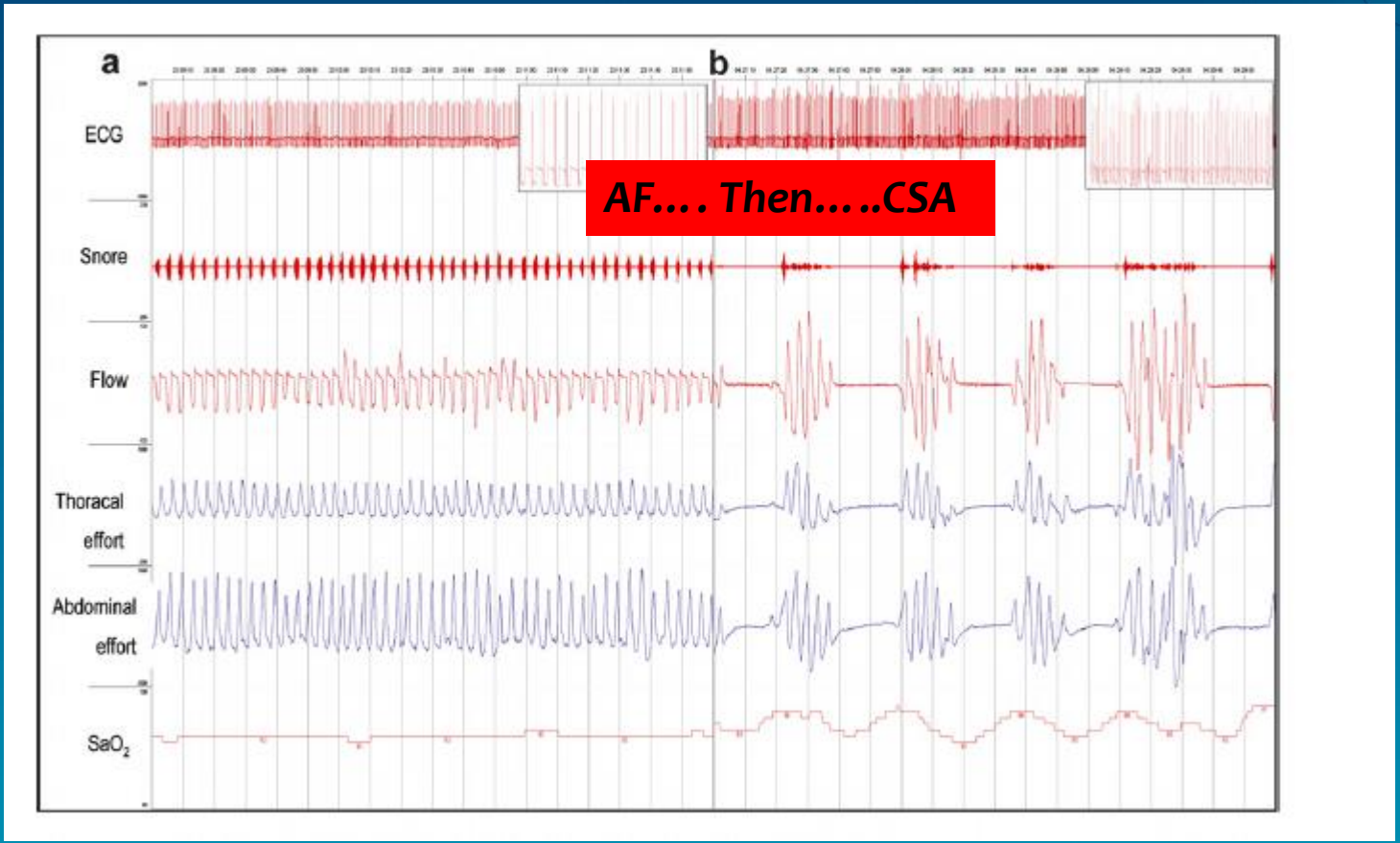
Predictor	Events/Total	Minimally Adjusted OR* (95% CI)	Multivariable Adjusted OR† (95% CI)
Age <76 yr			
AHI per 5-unit increase	57/529	0.95 (0.86–1.06)	0.92 (0.82–1.04)
AHI <15	33/308	1.00 (reference)	1.00 (reference)
AHI ⩾15	24/221	0.96 (0.54–1.70)	0.79 (0.42–1.49)
OAHI per 5-unit increase‡	57/529	0.95 (0.85–1.06)	0.92 (0.82–1.04)
CAI <5	53/500	1.00 (reference)	1.00 (reference)
CAI ⩾5‡	4/29	1.33 (0.44–3.99)	1.22 (0.34–4.41)
No CSA-CSR	51/486		
CSA-CSR‡	6/43	1.36 (0.55–3.40)	1.45 (0.52–4.07)
Percentage of total sleep time with Sa_{O_2} <90%			
<1%	29/276	1.00 (reference)	1.00 (reference)
1% to <3.5%	11/139	0.69 (0.33–1.45)	0.61 (0.28–1.35)
3.5% to <10%	12/61	2.13 (0.99–4.57)	1.74 (0.71–4.24)
⩾10%	5/53	0.78 (0.27–2.23)	0.57 (0.18–1.82)
Age ⩾76 yr			
AHI per 5-unit increase	42/314	**1.20 (1.08–1.33)**	**1.22 (1.08–1.39)**
AHI <15	16/183	1.00 (reference)	1.00 (reference)
AHI ⩾15	26/131	**2.91 (1.43–5.90)**	**2.64 (1.16–6.00)**
OAHI per 5-unit increase‡	42/314	**1.17 (1.05–1.30)**	1.13 (0.98–1.29)
CAI <5	35/295	1.00 (reference)	1.00 (reference)
CAI ⩾5‡	7/19	**4.86 (1.72–13.72)**	**9.97 (2.72–36.50)**
No CSA-CSR	34/289	1.00 (reference)	1.00 (reference)
CSA-CSR‡	8/25	**3.88 (1.50–10.07)**	**6.31 (1.94–20.51)**
Percentage of total sleep time with Sa_{O_2} <90%			
<1%	14/140	1.00 (reference)	1.00 (reference)
1% to <3.5%	13/97	1.34 (0.58–3.09)	1.69 (0.65–4.40)
3.5% to <10%	7/39	1.93 (0.67–5.51)	2.24 (0.69–7.30)
⩾10%	8/38	2.38 (0.87–6.52)	2.68 (0.77–9.34)

CSA may pose a greater risk in older pt for AF than OSA

May AM et al. Am J Respir Crit Care Med 2016; 193: 783-91

Impact of AF on CSA

Periodic breathing patterns ***few minutes following*** the onset of intermittent AF with a fast ventricular response and a heart rate up to 140 bpm, left ventricular diastolic dysfunction



S. Rupprecht et al. / Sleep Medicine 9 (2008) 462–464

Impact of AF on OSA

How AF could theoretically cause CSA and worsen OSA

immediate effects of tachycardia-induced and elevate LA pressure

⇩

left ventricular dysfunction and diastolic dysfunction

⇩

reduction of cardiac output

⇩

raised pulmonary capillary wedge pressure

⇩

trigger hyperventilation and hypocapnia through stimulation of pulmonary vagal irritant receptors with breathing instability

Restoration of normal sinus rhythm leads to improvement in OSA/CSA severity ?... unclear

OSA and Stroke Risk

Table 5: OSA and stroke risk.

Investigator	Number of patients	Primary endpoints	Mean followup (yrs)	Control for AF	Risk factor adjustments	Results for stroke
Boden-Albala et al. (2012) [92]	2088	Ischemic stroke, MI, death	5.1	Yes	Age, sex, race, education, WC, systolic and diastolic BP, fasting glucose, HDL, alcohol, smoking, physical activity, PVD, CAD, total cholesterol/HDL level, depression, and medication usage.	HR for ischemic stroke in patients with significant dozing was 2.74 (1.38–5.43); HR for all stroke, 3.00 (1.57–5.73)
Redline et al. (2010) [93]	5422	Ischemic stroke	8.7	No	Age, race, BMI, smoking, BP, antihypertensives, DM.	Adjusted HR for stroke in men with severe OSA was 2.86 (1.10–7.39)
Munoz et al. (2006) [94]	394	Stroke	4.5	Yes	Sex.	Adjusted HR for stroke in OSA patients was 2.52 (1.04–6.10)
Yaggi et al. (2005) [95]	1022	Stroke or death	3.4	Yes	Age, race, sex, smoking, alcohol consumption, BMI, AF, HTN, and lipids.	Unadjusted RR for stroke in OSA was 3.02 (1.27–7.21), death adjusted RR, 1.70 (0.92–3.16)
Arzt et al. (2005) [45]	1189	Stroke	4	No	Age, sex, and BMI.	Fully adjusted OR for stroke in severe OSA was 3.08 (0.74–12.81)
Marin et al. (2005) [96]	1010	Fatal MI, stroke	10.1	No	Age, CV disease, DM, HTN, lipid disorders, smoking, alcohol use, BP, glucose, lipid levels, and CV drugs.	OR for fatal MI or stroke in untreated severe OSA was 2.87 (1.17–7.51)
Mooe et al. (2001) [97]	408	Death, cerebrovascular events, MI	5.1	No	Age, sex, BMI, HTN, DM, left ventricular function, and coronary intervention.	OR for stroke in moderate OSA patients was 2.62 (1.26–5.46), in severe OSA patients, 2.98 (1.43–6.20)
Hu et al. (2000) [98]	71,779 women	Stroke, coronary heart disease, fatal cardiovascular events	8	No	Age, BMI, cigarette smoking, DM, hypercholesterolemia, menopausal status, family history of MI before age 60, alcohol consumption, multivitamin and vitamin E use, physical activity, number of hours sleeping, and sleep position.	Age-adjusted total stroke RR for occasional snorers, 1.60 (1.21–2.12); for regular snorers 1.88 (1.29–2.74). Multivariate adjusted RR for occasional snorers, 1.42 (1.07–1.89); for regular snorers RR 1.35 (0.91–1.99)

MI: myocardial infarction; WC: waist circumference; BP: blood pressure; HDL: high density lipoprotein; PVD: peripheral vascular disease; CAD: coronary artery disease; BMI: body mass index; HR: hazard ratio; DM: diabetes mellitus; HTN: hypertension; RR: relative risk; OR: odds ratio; CV: cardiovascular.

The ralationship between OSA and Atrial Fibrillation: a Complex Interplay .Pulmonary Medicine 2013

Effect of Obstructive Sleep Apnea on Frequency of Stroke in Patients With Atrial Fibrillation

5,138 patients screened for OSA, 402 (7.7%) had AF, Retrospective
332 pts met inclusion criteria (AF pts with OSA)

Ischemic stroke was *more common in patients with OSA compared* with patients without (25.4% vs 8.2% respectively, p [0.006)

After controlling for age, male gender, and coronary artery disease the association between OSA and stroke remained statistically significant, with an adjusted OR of ***3.65*** (95% CI 1.252 -10.623)

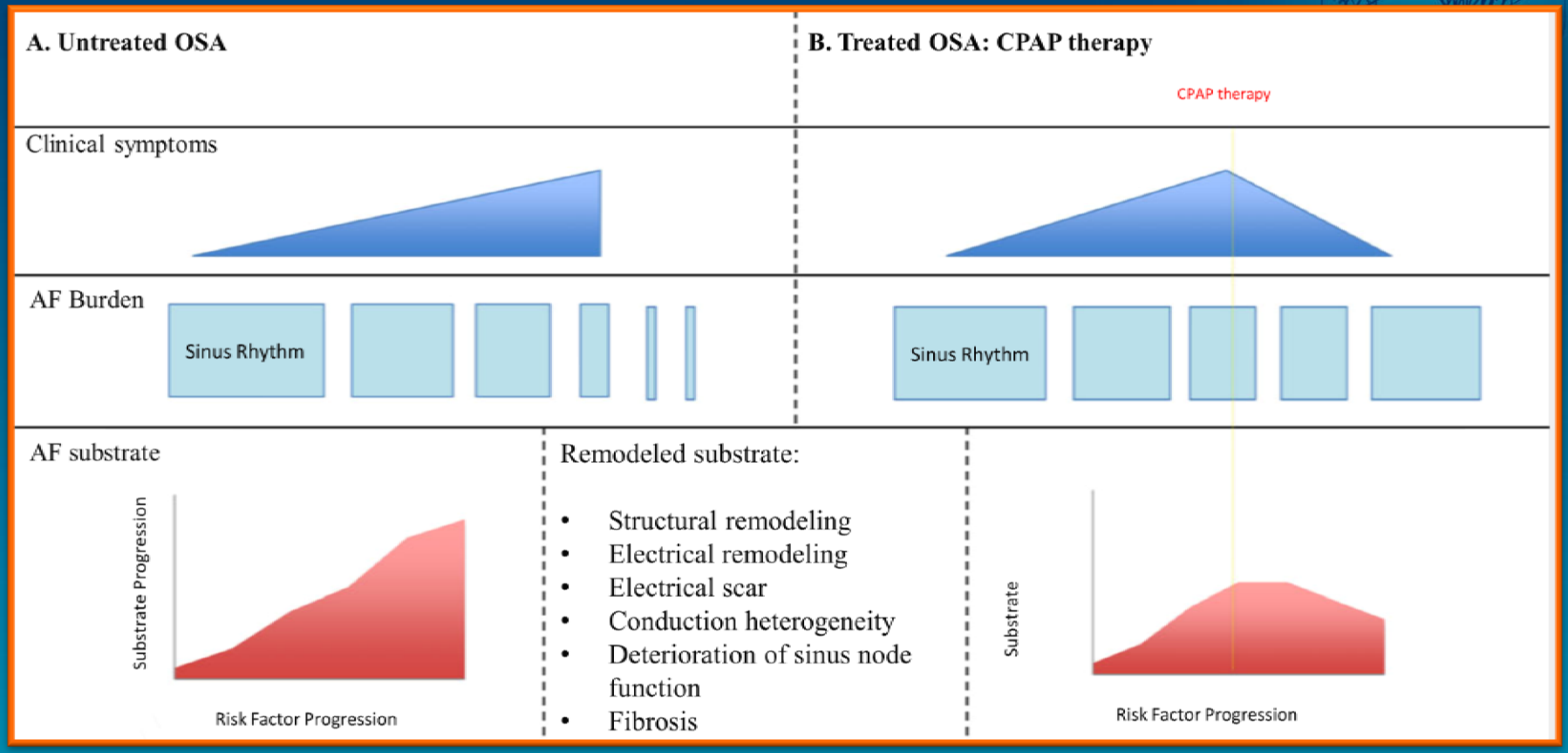
Table 4
Odds ratio of stroke across CHA_2DS_2VASc groups by obstructive sleep apnea status

CHA_2DS_2VASc score (number of patients)	Odds ratio	95% Confidence interval
0 (n=29)	1.62	1.15 - 2.26
1 (n=52)	1.32	0.14 – 12.51
2 (n=61)	1.26	1.09 – 1.44
3 (n=69)	1.76	0.34 – 9.10
4 (n=60)	1.46	1.22 – 1.75
5 (n=48)	2.65	0.30 – 24.14
6 (n=13)	1.20	0.07 – 3.04

OSA is an independent risk factor for stroke in a population of patients with AF

Yaranov DM Am J Cardiol 2015;115:461e5

Impact of CPAP therapy on the AF substrate, AF burden, and clinical symptoms



Nalliah et al . J Cardiovasc Electrophysiol, 2016; 27: 1001-10

Results in AF in patients with OSA
(inteventional study – CPAP therapy)

KANAGALA [2003]	39 Pts with AF and OSA (79 controls with only AF)	**Recurrence of AF 12 months after cardioversion** 82% in OSA patients without CPAP therapy 42% in OSA patients with CPAP therapy, (53% in control subjects)
ABE [2010]	1350 pts with OSA (44 no SBD)	CPAP significantly reduced nocturnal paroxysmal AF and supraventricular ectopies from 14% to 4%
CRAIG [2009]	83 pts OSA therapeutic CPAP vs sub-therapeutic CPAP	CPAP does not affect frequency of AA

Rossi VA et al. Eur Respir J 2013; 41: 1439-1451

Available evidence supports the role of effective OSA therapy in reducing the risk of AF recurrence

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

Obstructive Sleep Apnea and the Recurrence of Atrial Fibrillation
Ravi Kanagala, Narayana S. Murali, Paul A. Friedman, Naser M. Ammash, Bernard J. Gersh, Karla V. Ballman, Abu S. M. Shamsuzzaman and Virend K. Somers

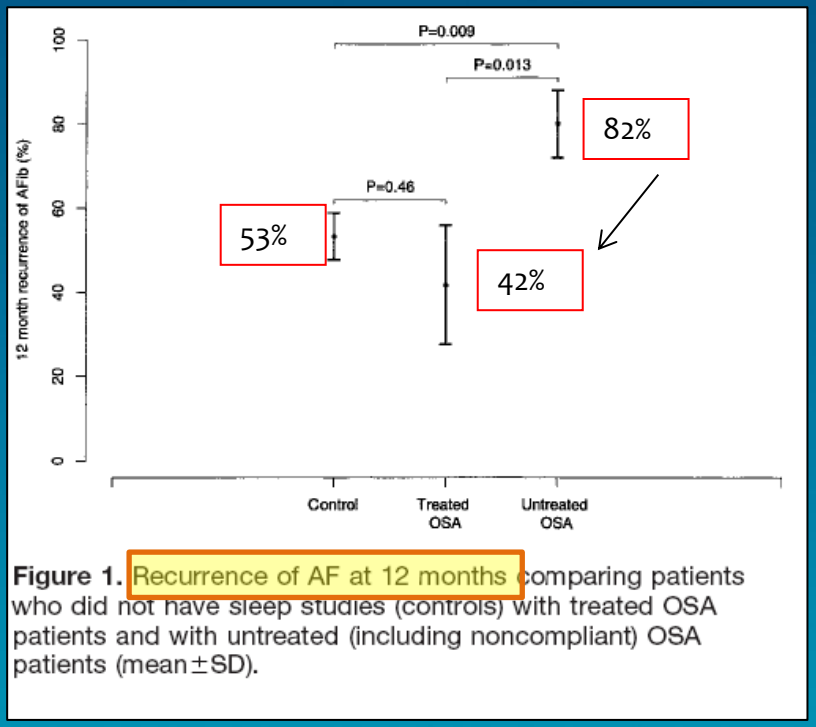


Figure 1. Recurrence of AF at 12 months comparing patients who did not have sleep studies (controls) with treated OSA patients and with untreated (including noncompliant) OSA patients (mean ± SD).

Higher recurrence of AF after cardioversion if OSA remains untreated:

- OSA Not treated: 82%
- OSA Treated: 42%

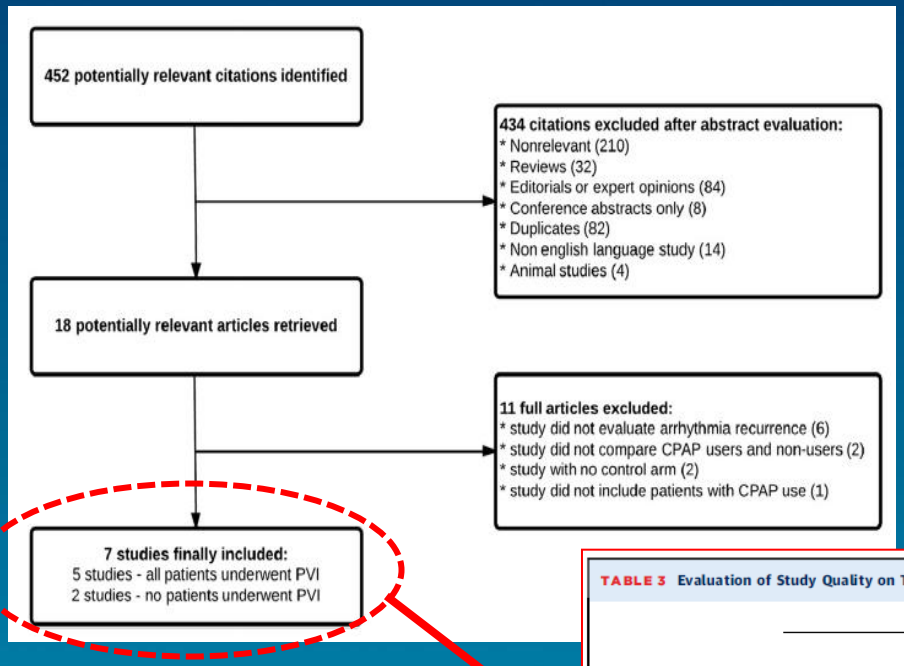
- 39 individuals with previous diagnosis of OSA and 79 controls without previous sleep study

- 27 of the 39 OSA not receiving any CPAP therapy (n=25) or noncompliant with CPAP (n=2) → **untreated OSA group**
- 12 patients who used CPAP appropriately →**treated OSA group**

Kanagala R et al. Circulation 2003

Meta-analysis - OSA treatment on AF recurrence

1. AF recurrence in CPAP users vs non-users with OSA
2. AF recurrence CPAP users/non-users after Pulmonary Veins Isolation



There have been no randomized studies on the effect of CPAP on AF recurrence

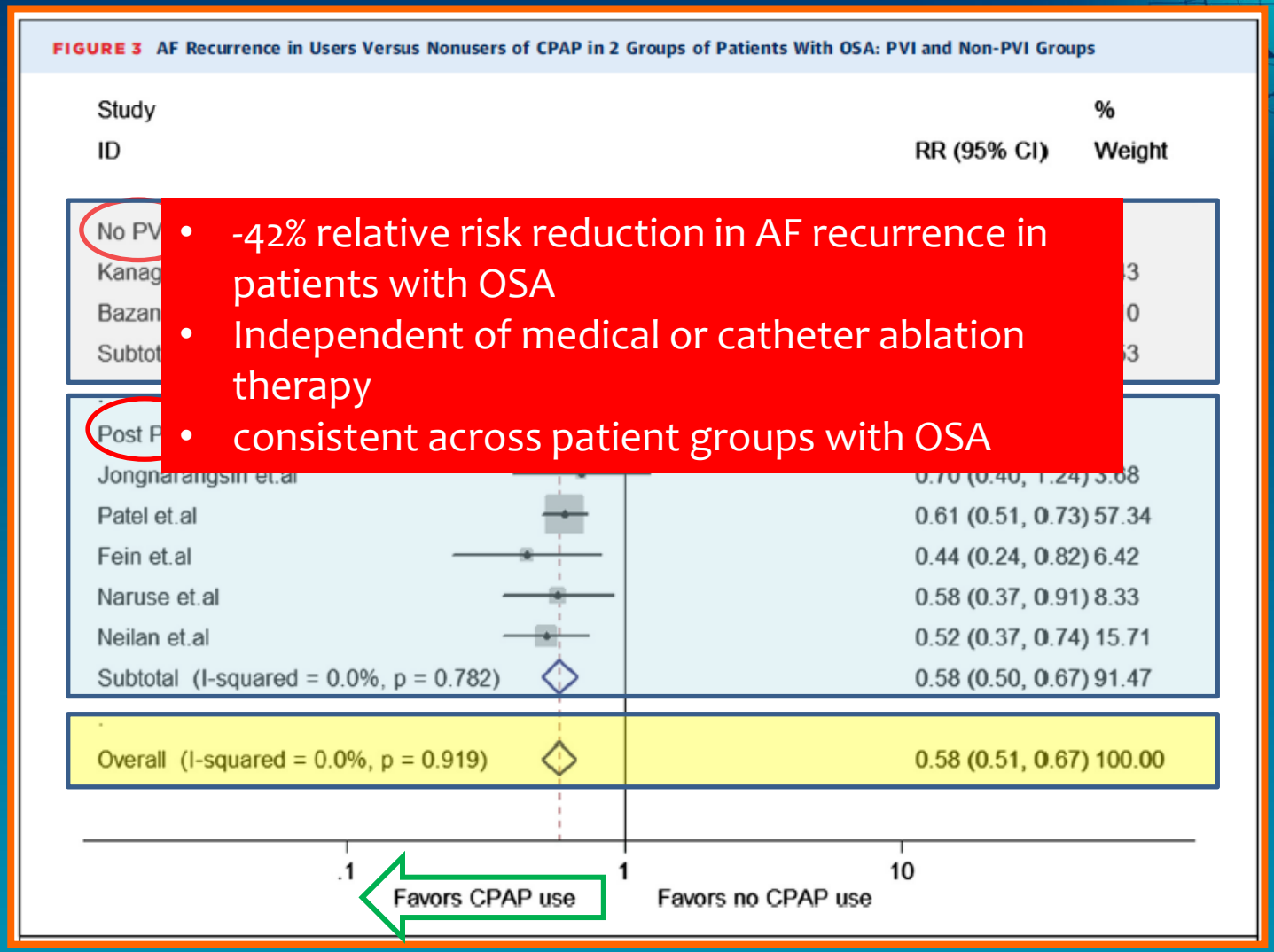
TABLE 3 Evaluation of Study Quality on The Basis of Newcastle Ottawa Scale

	Selection				Comparability	Outcome				
First Author (Ref. #)	Representativeness	Selection of the Nonexposed Cohorts	Ascertainment	Endpoint Not Present at Start	Comparability (Confounding)	Assessment of Outcome	Follow-Up Duration	Adequacy of Follow-Up	Total	Quality
Fein et al. (17)	*	*	*	*	*	*	*	*	8	High
Patel et al. (15)	*	*	*	*	0	*	*	*	7	High
Naruse et al. (18)	*	*	*	*	0	*	*	*	7	High
Neilan et al. (19)	*	*	*	*	*	*	*	*	8	High
Kanagala et al. (13)	*	*	*	*	*	*	*	*	8	High
Bazan et al. (16)	0	*	*	*	0	*	*	*	6	High
Jongnarangsin et al. (14)	*	*	*	*	0	*	*	*	7	High

*Criteria met.

Shukla A et al. J Am Coll Cardiol EP 2015; 1: 41-51

CPAP benefit in AF recurrence reduction



- -42% relative risk reduction in AF recurrence in patients with OSA
- Independent of medical or catheter ablation therapy
- consistent across patient groups with OSA

Shukla A et al. J Am Coll Cardiol CE 2015; 1: 41-51

Impact of OSA and CPAP therapy on outcomes in patients with AF

Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)

cPAP: reduction in AF progression

Table IV. Association of CPAP treatment and 2-year outcomes

Outcome	CPAP (n = 937) No. of events (events/100 patient-years)	No CPAP (n = 687) No. of events (events/100 patient-years)	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
All-cause death	68 (4.44)	54 (4.86)	0.92 (0.67-1.25)	.58	1.10 (0.78-1.54)	.60
First hospitalization (all-cause)	471 (43.9)	329 (41.9)	1.05 (0.93-1.18)	.42	1.10 (0.97-1.24)	.14
CV death, MI, stroke/TIA	57 (3.78)	41 (3.73)	1.02 (0.68-1.52)	.94	1.15 (0.73-1.82)	.55
Major bleeding	71 (4.81)	43 (3.99)	1.20 (0.85-1.71)	.29	1.45 (0.99-2.11)	.06

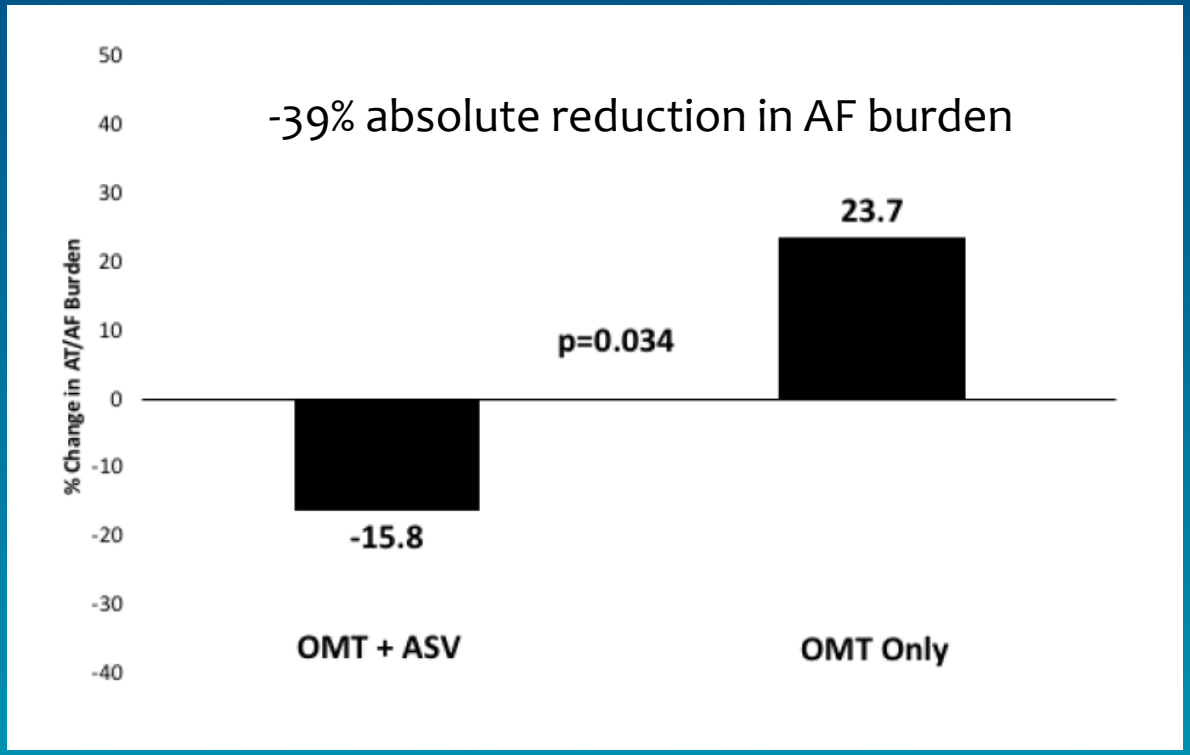
Outcome	CPAP (n = 602) No. of events (percent)	No CPAP (n = 411) No. of events (percent)	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Progression of AF type	94 (16)	75 (18)	0.74 (0.55-0.99)	.04	0.66 (0.46-0.94)	.02

Holmqvist et al. Am Heart J 2015;169:647-654

Impact of ASV and CPAP therapy on outcomes in patients with AF

Prospective substudy as part of the randomized Cardiovascular Improvements with ASV Therapy in Heart Failure (CAT-HF)

First randomized assessment of ASV therapy on AF burden in patients with sleep apnea



126 pts heart failure and reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) and an apnea-hypopnea index (AHI) ≥15 due to obstructive and/or central sleep apnea were eligible for randomization in CAT-HF

Piccini et al HR 2019 Volume 16, Issue 1, Pages 91–97

Current Clinical Practice Recommendations

- ***Interrogation for clinical symptoms*** of OSA and screening for OSA in all patients diagnosed with AF (class IIa, level B), particularly those considered for a rhythm control strategy

- ***Sleep study evaluation*** may be reasonable in patients with AF who do not report daytime sleepiness

- ***Initiation of continuous positive airway pressure*** treatment to re- duce AF recurrences and improve AF treatment results (class IIa, level B)

Calkins et al. Heart Rhythm.2017;14 (10):e275-e444
Kirchhof et al Eur Heart J. 2016;37(38):2893-2962

Uncertainties and Controversies

- Do patients with AF should routinely be screened for OSA?
- Do randomized clinical trials confirm that treatment of OSA prevents incident and recurrent AF?
- What level of severity of sleep apnea should be used to determine the need for treatment?
- Does position-dependent OSA with apneas just in the supine position represent a treatment target in patients with AF?
- What is the role of CPAP treatment in older patients with AF?

Conclusions

- Epidemiologic data demonstrate a strong relationship of SA with AF
- Mechanistic studies together with correlations of apnea severity with AF persistence/burden imply that SA directly impacts the AF substrate
- SA increase stroke risk in AF patients
- Treatment of SA carries the potential to modify the AF substrate and improve its clinical profile

Conclusions

- Studies that have evaluated the impact of CPAP/AVS therapy on AF have been small and observational in nature with multiple study limitations:
  - variable techniques utilized to diagnose OSA
  - control groups are frequently unscreened
  - compliance data are not always well evaluated

Conclusions

- The existing evidence base advocates for screening and treatment of SA in cases of newly diagnosed AF and in patients with RFs

- Need for high-quality data in the form of a randomized trial that definitively demonstrates the benefit and effect size of cPAP/AVS therapy