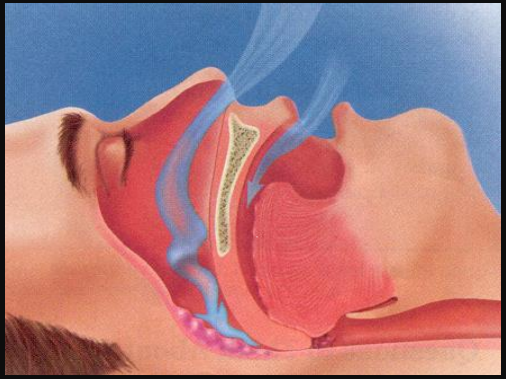
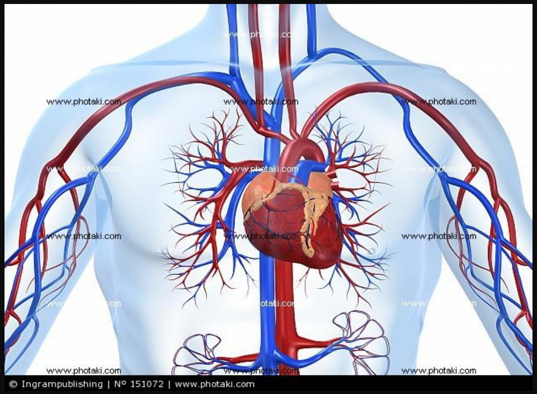




Sleep Disorders and Cardiac Arrhythmias

Turning the Beat Around

Reena Mehra MD, MS, FCCP, FAASM

Director, Sleep Disorders Center Research

Professor of Medicine

Sleep Disorders Center, Neurologic Institute

Respiratory Institute

Heart and Vascular Institute

Department of Molecular Cardiology, Lerner Research Institute

Cleveland Clinic

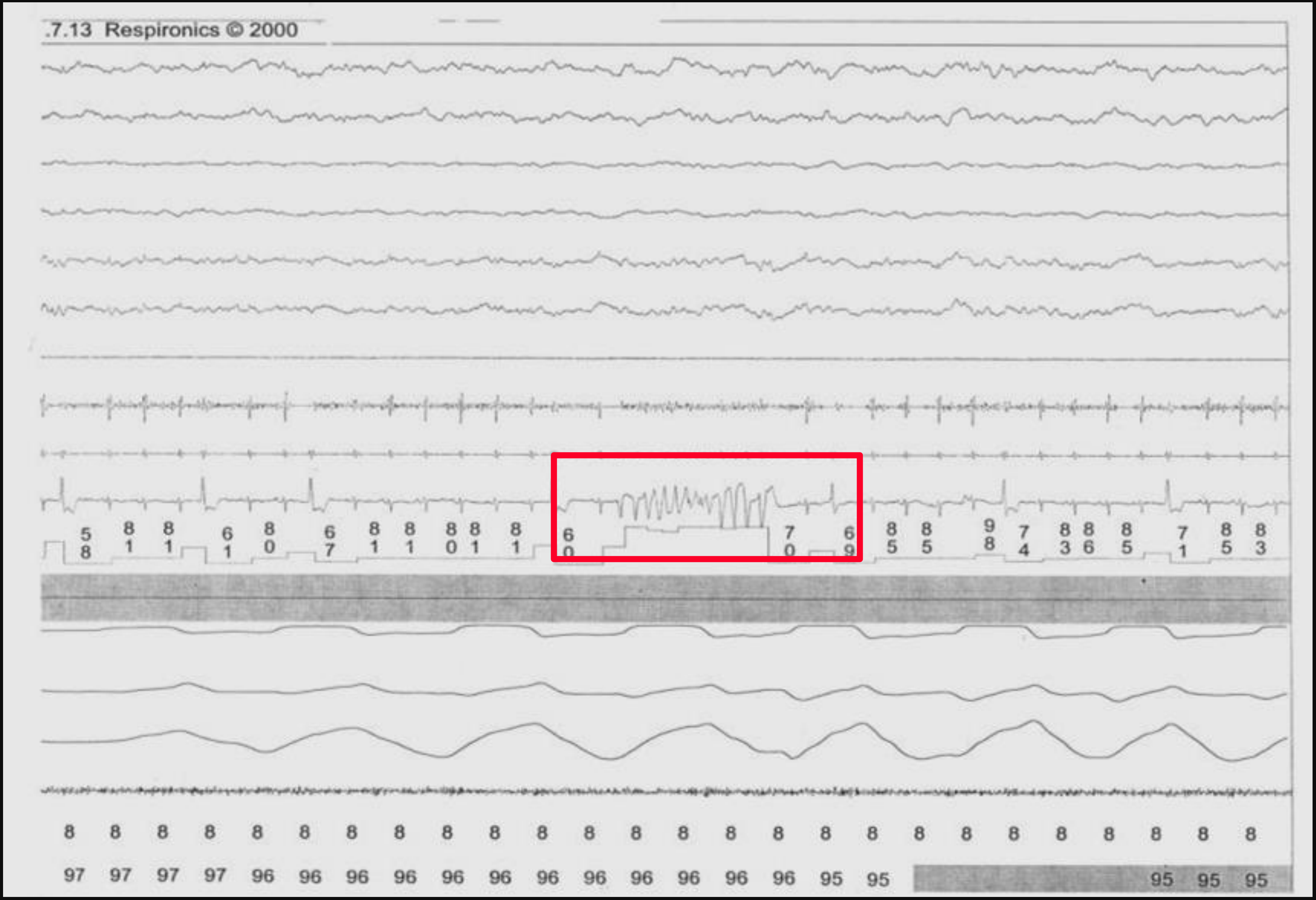
May 4, 2018

Sleep and Cardiac Arrhythmias

- Understand the mechanisms underlying sleep disorders and cardiac arrhythmia
- Discuss epidemiological studies informing current state of knowledge of sleep disorders and cardiac arrhythmias and sudden cardiac death
- Review future directions to address existing knowledge gaps

Clinical Case

- 61- year old male with history of coronary artery disease and dilated cardiomyopathy (EF=20%) undergoes a split-night study at a hospital-based facility
- Sleep apnea was suspected on the basis of:
  - Snoring
  - Occasional witnessed pauses during sleep



Mehra R, Strohl KP SLEEP 2004

Incidence of Serious Adverse Events During Nocturnal Polysomnography

Reena Mehra, MD, MS, Kingman P. Strohl, MD

Center for Sleep Disorders Research, Louis Stokes DVA Medical Center, Case Western Reserve University Cleveland, OH

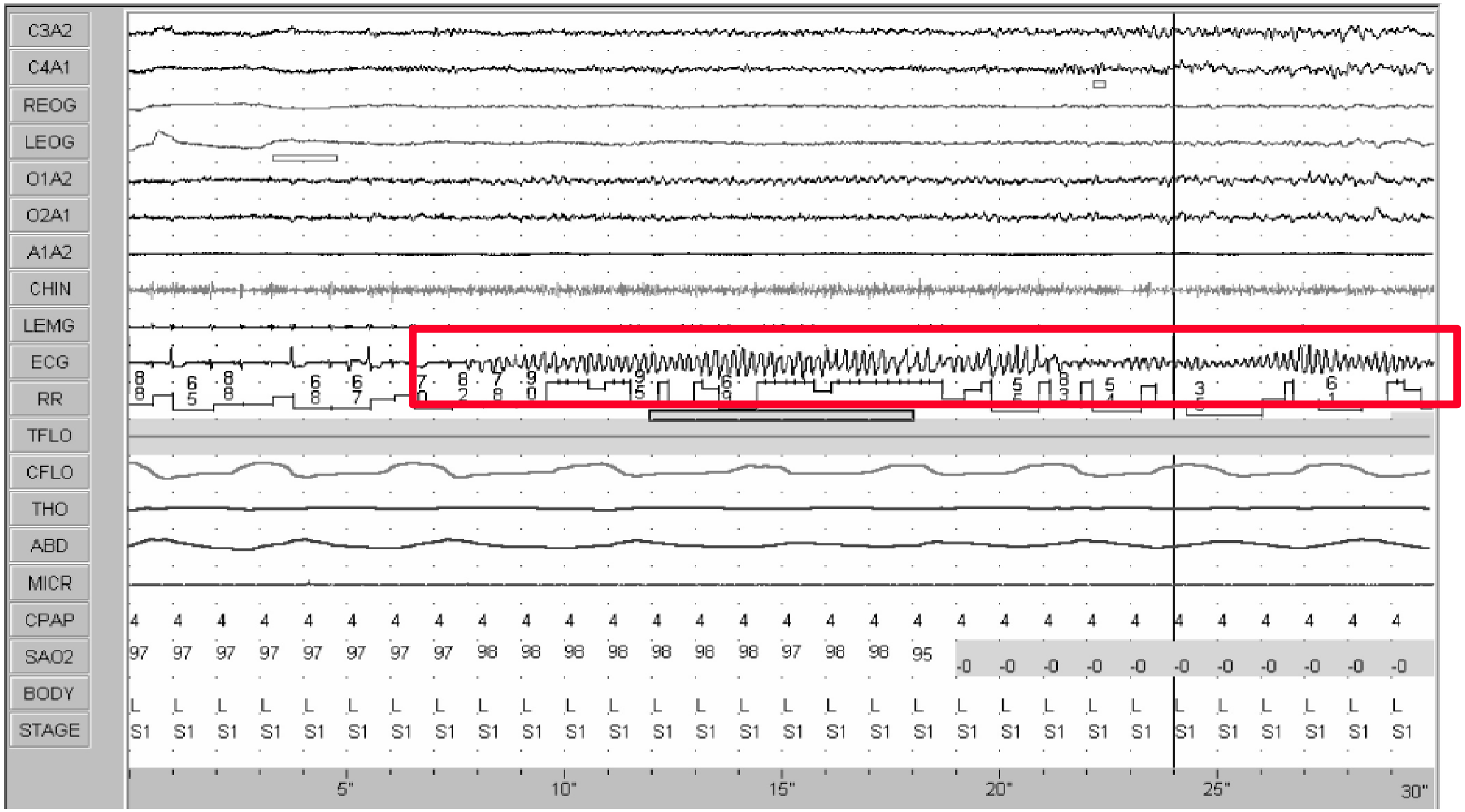
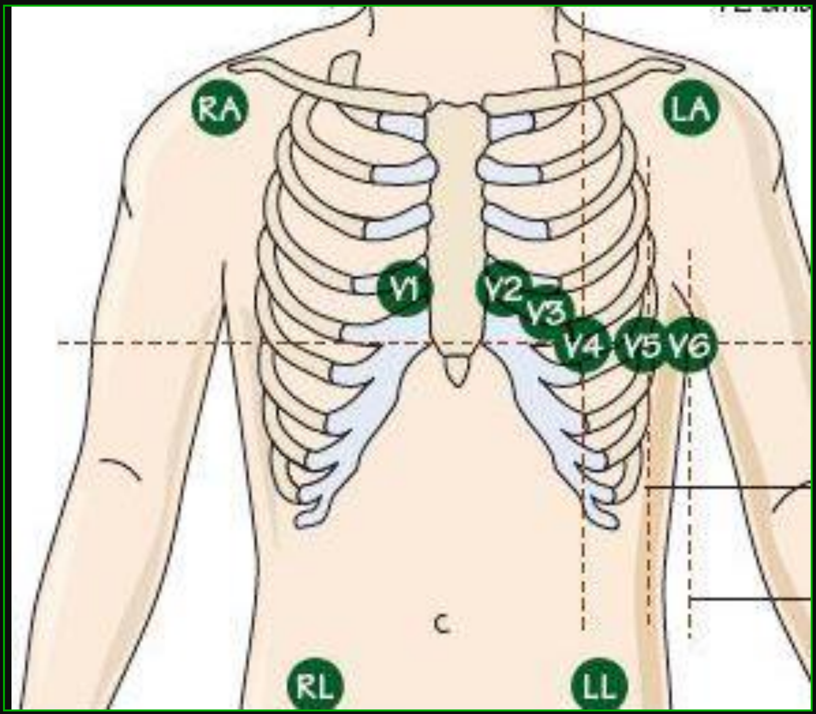
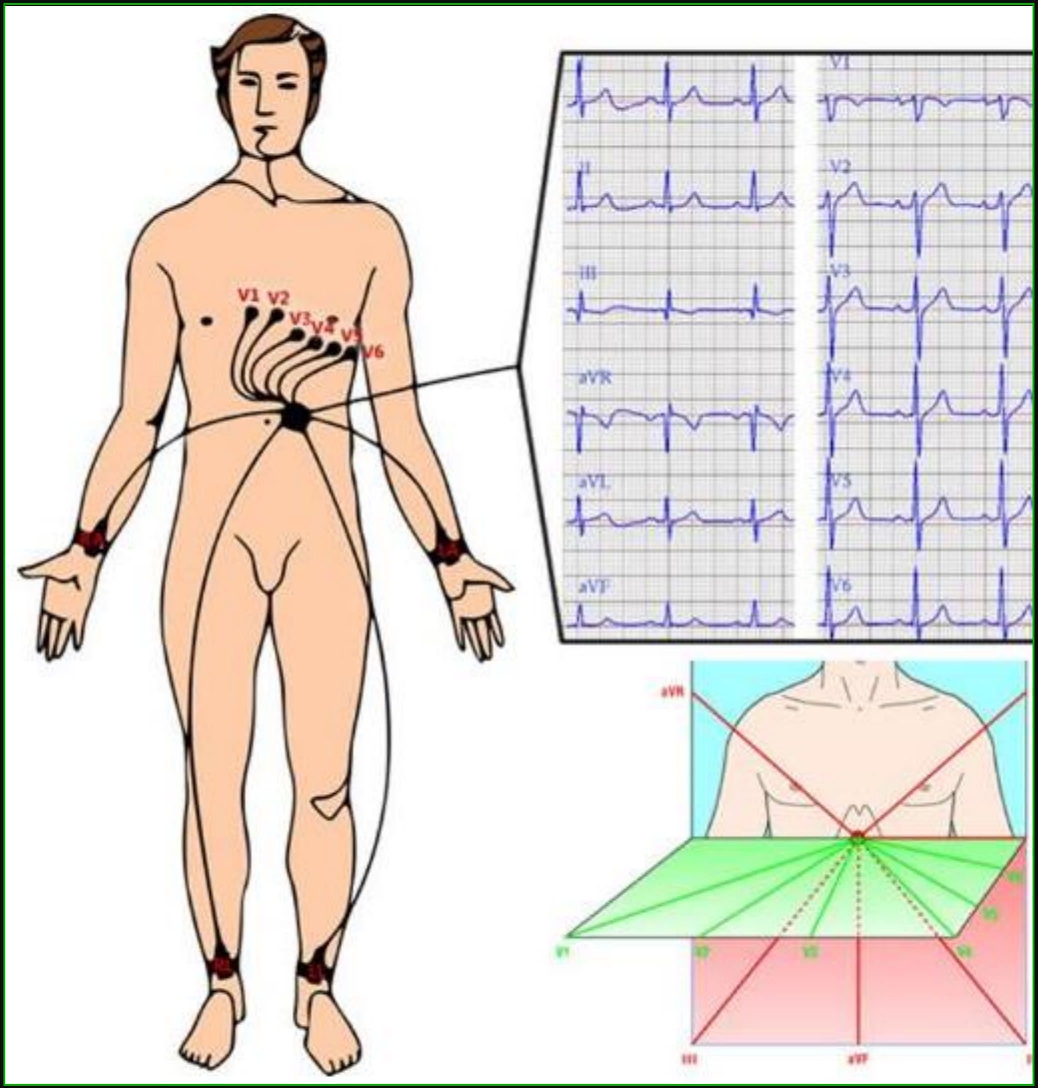


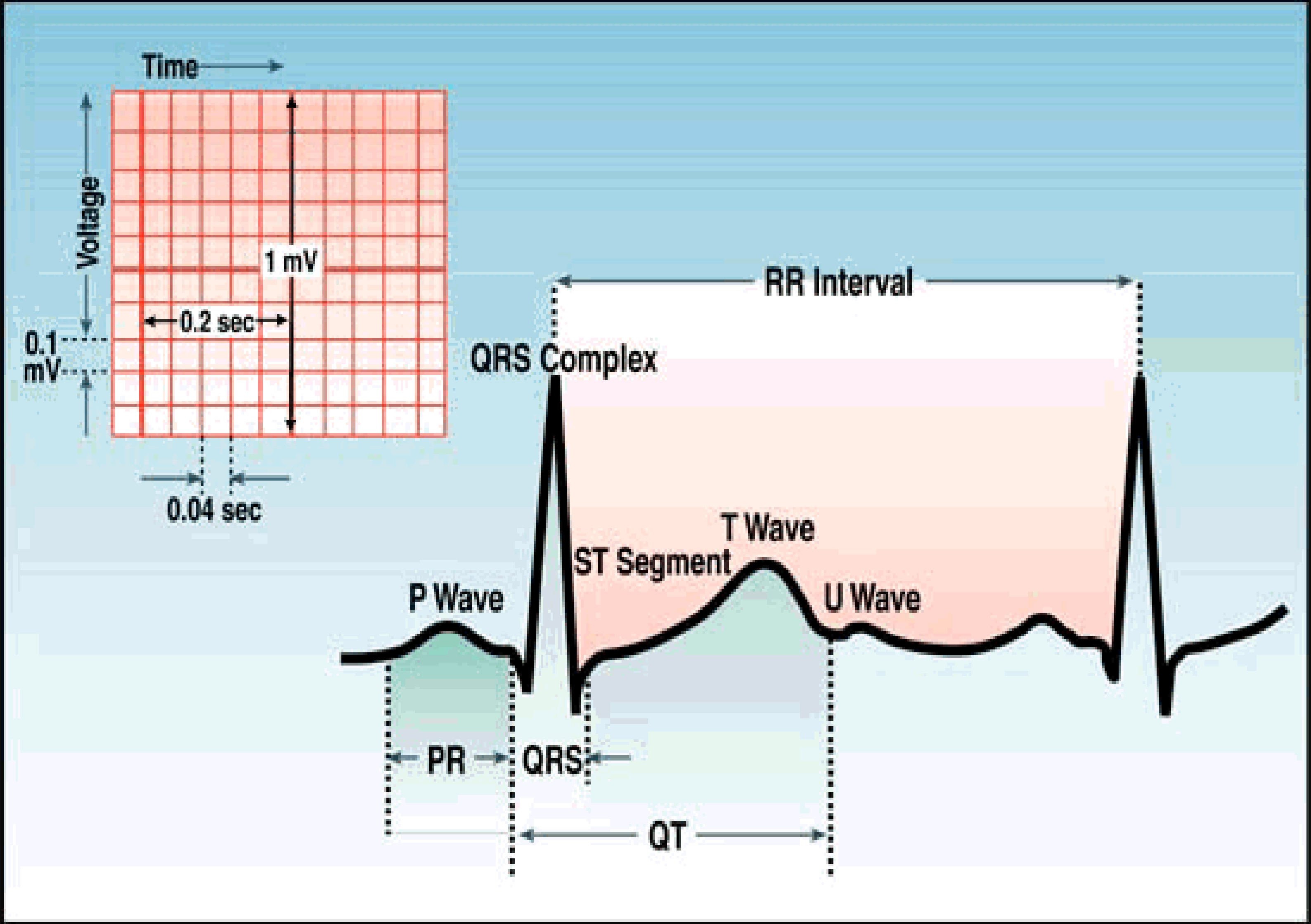
Figure 2—The record shows the terminal episode of polymorphic sustained ventricular tachycardia/fibrillation on the electrocardiogram channel (noted by the bar) occurring in stage 1 sleep during continuous positive airway pressure (CPAP) titration (current level, 4 cm H_2O). C3A2, C4A1, O1A2, and O2A1 refer to electroencephalogram channels; REOG and LEOG, right and left electrooculogram; LEMG, left electromyogram; RR, heart rate; CFLO, airflow; THO, thoracic effort; ABD, abdominal effort; MICR, microphone; SAO2, oxygen saturation; BODY, body position; and STAGE, sleep stage.

The Electrocardiogram



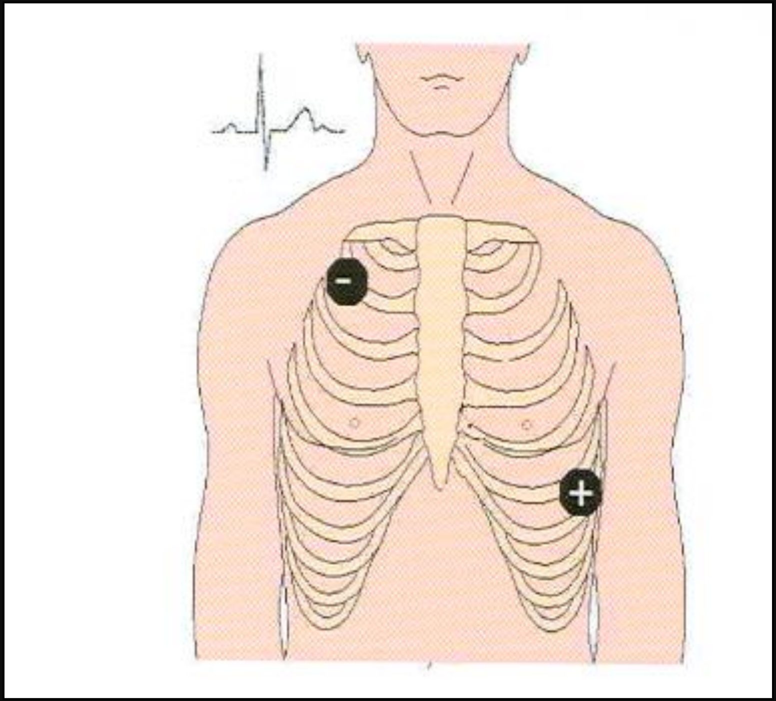


- 12-lead ECG recorded from the body surface
- Reflects summation of the electrical activity of the heart


Time
Voltage
1 mV
0.2 sec
0.1 mV
0.04 sec
RR Interval
QRS Complex
T Wave
ST Segment
P Wave
U Wave
PR
QRS
QT

ECG Electrode Placement

- **A single electrograph Lead II is recommended.**
  - This classically a derivation consisting of an electrode at the R arm and L leg.
  - A modified torso electrode placement is now recommended (R shoulder and L hip)



Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Sympathetic nerve activity and simulated diving in healthy humans

Abu Shamsuzzaman [a,b,*], Michael J. Ackerman [b], Fatima Sert Kuniyoshi [b], Valentina Accurso [b], Diane Davison [b], Raouf S. Amin [a], Virend K. Somers [b]

[a] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b] Mayo Clinic, Rochester, MN, USA

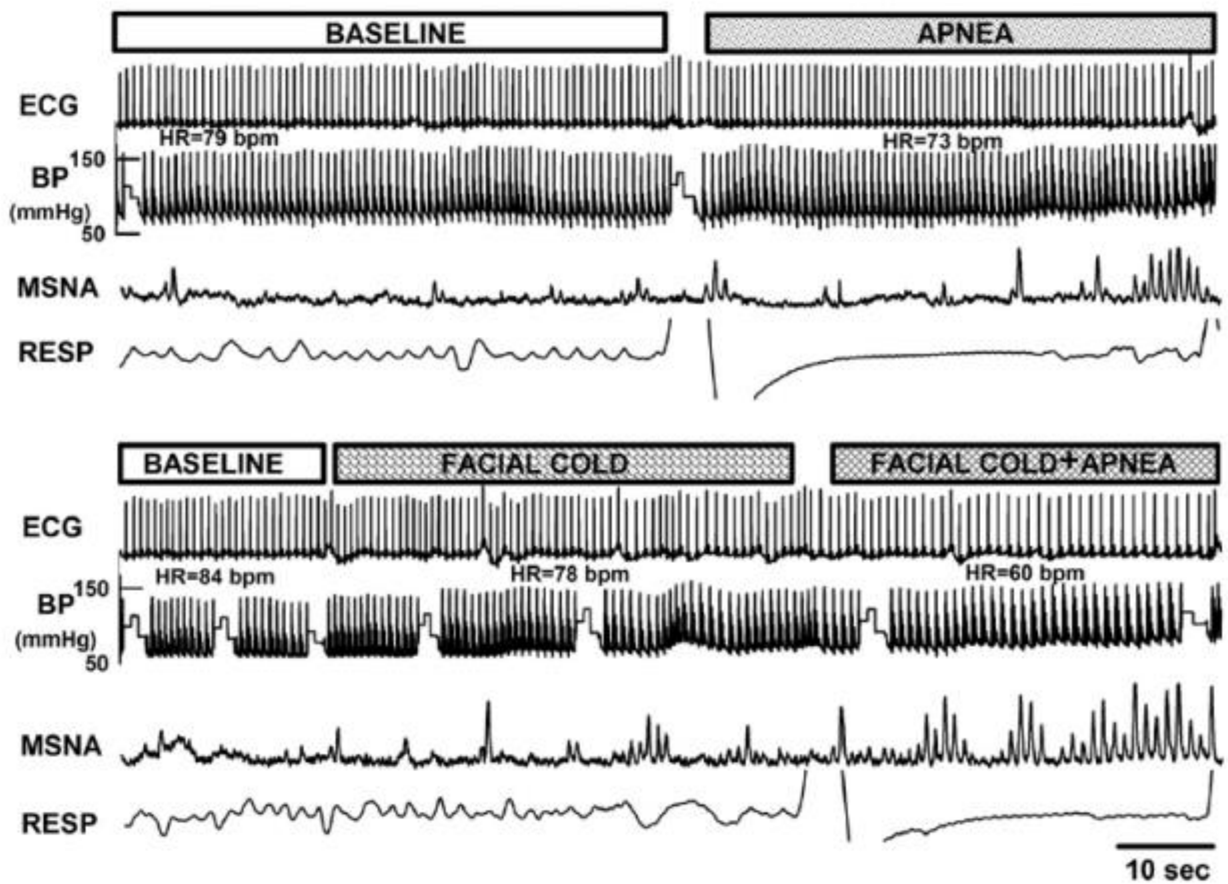
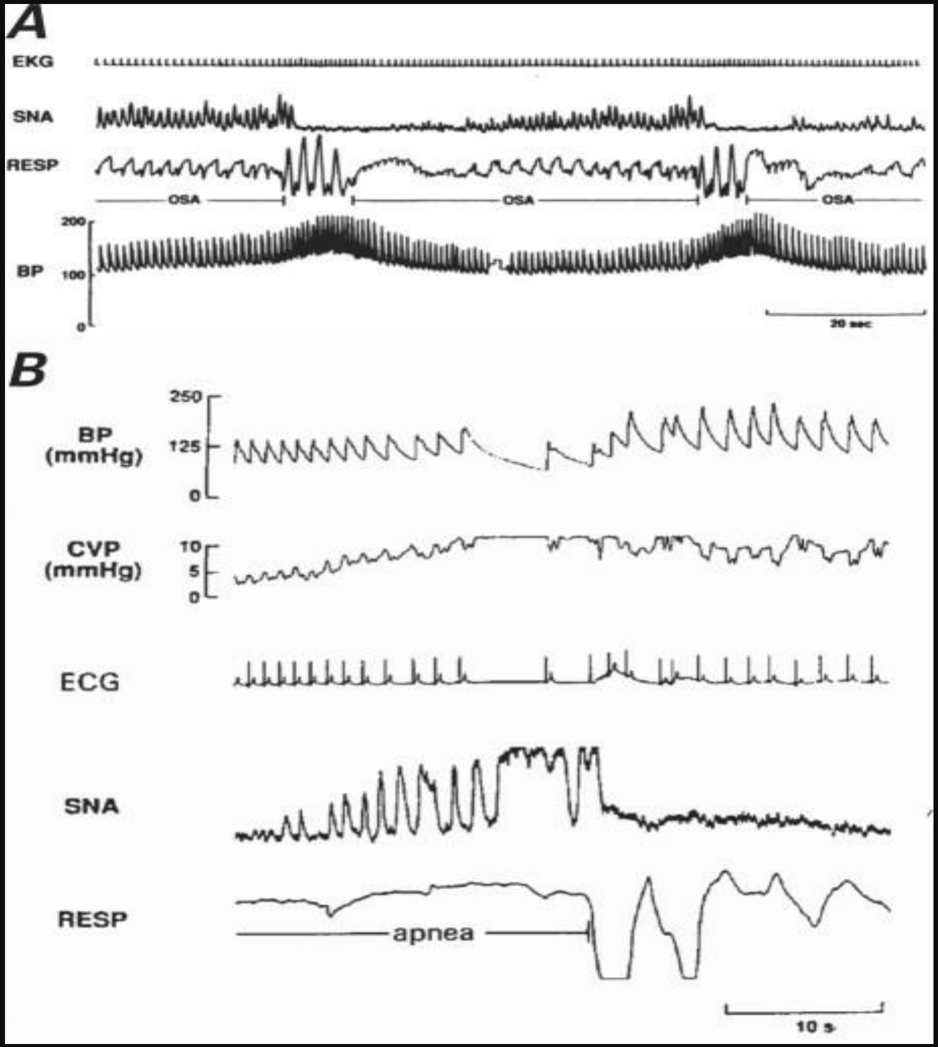


Fig. 1. Original recordings of ECG, BP, MSNA, and respiration during baseline, apnea, facial cold, and simulated diving (facial cold and apnea). Note increase in MSNA with bradycardia during simulated diving.

Mammalian Diving Reflex Pro-Arrhythmic?

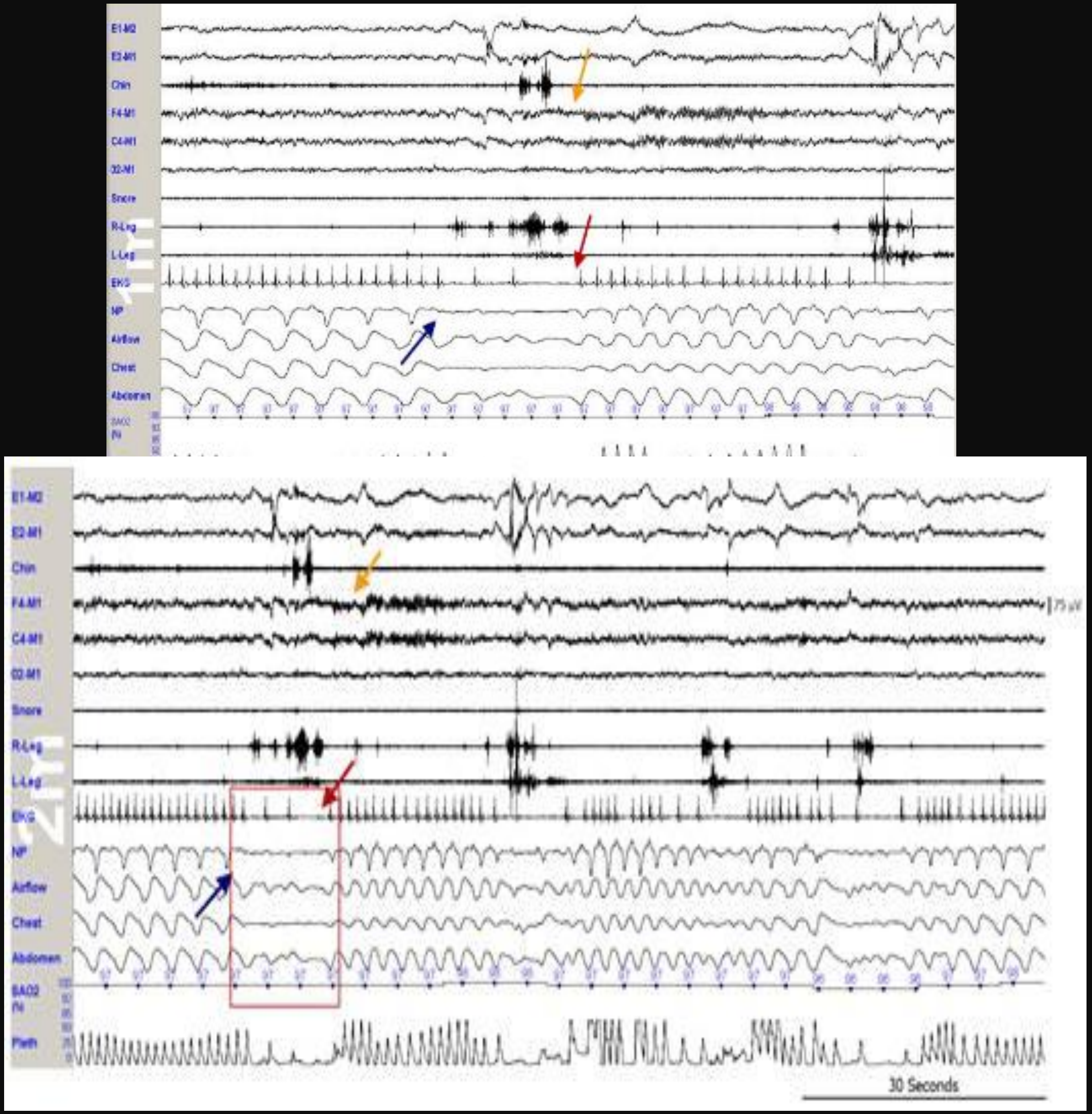


- Activation of diving reflex occurs during apneic episodes OSA
- ANS responses may represent a trigger for arrhythmias and sudden cardiac death in those with vulnerable substrates
- Diving induced bradycardia associated with ventricular ectopic beats in healthy individuals
- Nasal intubation, suction, packing and facial immersion: simple versus serious or fatal cardiac arrhythmias

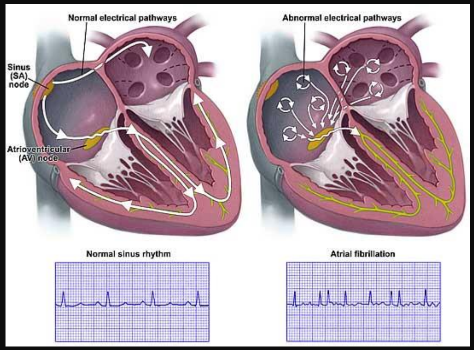
Whayne et al. Simulated diving in man: comparison of facial stimuli and response in arrhythmia. J Appl Physiol 1967
Allison DJ et al. Dangerous reflexes of the nose. Lancet 1977
Wildenthal et al. Diving reflex used to treat paroxysmal atrial tachycardia Lancet 1975

Obstructive Sleep Apnea and REM Sleep: Double Trouble for the Conditioned Heart

- 43 yo male marathon runner with snoring and fatigue
- Sinus bradycardia is noted often in endurance athletes along with left ventricular hypertrophy
- Increased parasympathetic tone, increase in vagal nerve activity and /or down-regulation of regulatory G-protein signaling causing increased heart sensitivity to acetylcholine
- High degree AV block in endurance athletes with inter-individual variability due to variation in localized hyperresponsivenss of the atrioventricular node to vagal tone



Atrial Fibrillation

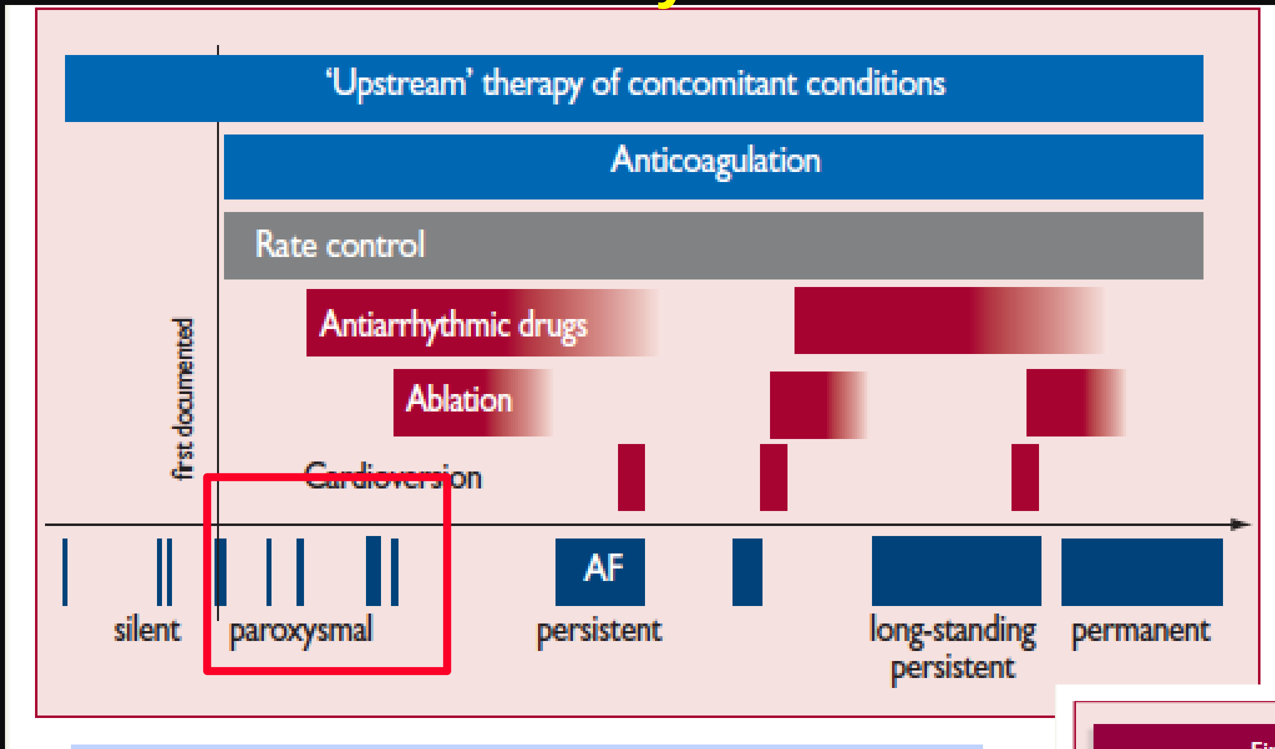


- Number of Americans afflicted by AF projected to increase from 2.3 million to more than 10 million by 2050
- Increasing incidence and prevalence of AF incompletely explained by aging population and established risk factors

Wolf PA AMJ 1996: 131: 4

- Unrecognized sleep apnea (estimated at 85%) may partially account for the current AF epidemic

Inflammation in Sleep Apnea and Paroxysmal Atrial Fibrillation

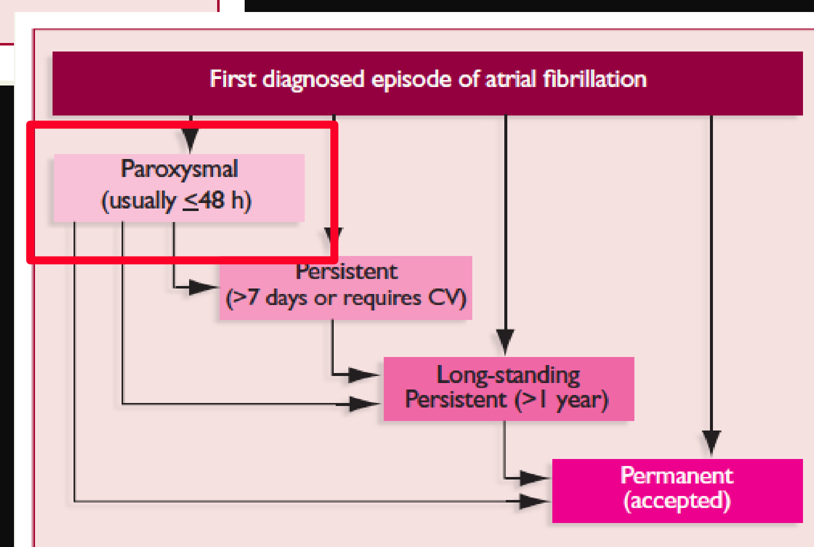


Progression of AF

- Silent and undiagnosed to paroxysmal and chronic forms at times symptomatic

Subtypes of AF

- Paroxysmal (self-terminating) to persistent [non-self-terminating or requiring cardioversion], persistent (> 1 year) and eventually permanent AF.
- First-onset AF may be first of recurrent attacks or permanent.

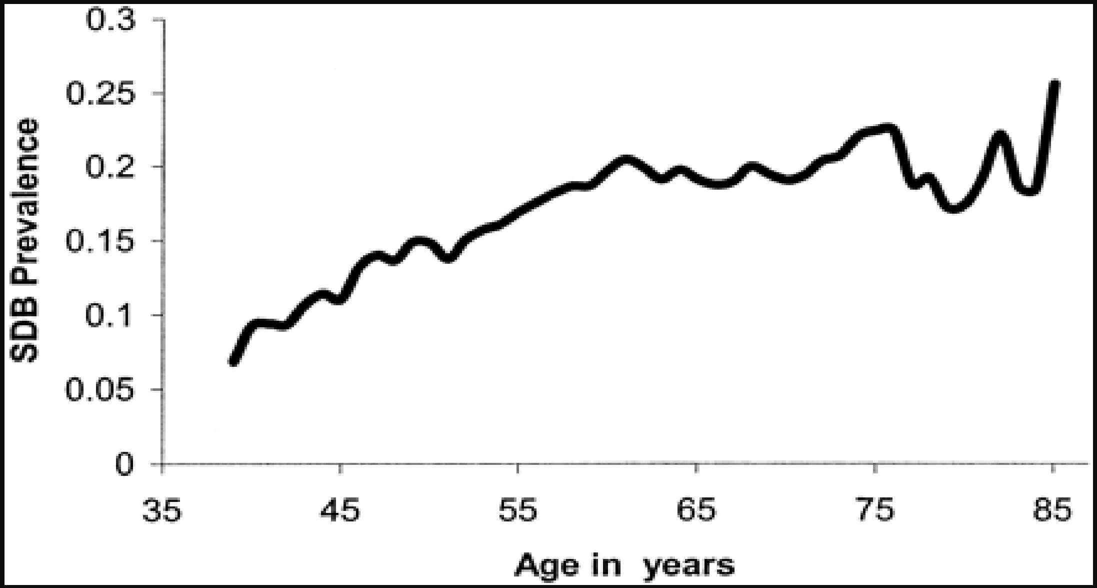


Camm AJ et al. European Heart Journal (2010)31, 2369–2429

Shared SDB and AF risk factors----

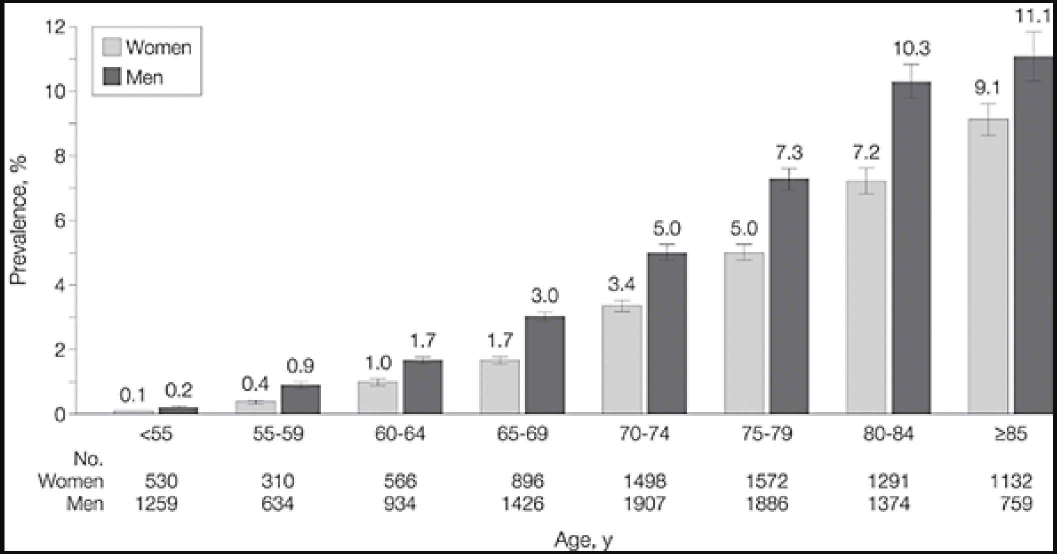
Age
Male gender
Obesity
Hypertension

SDB Prevalence and Age



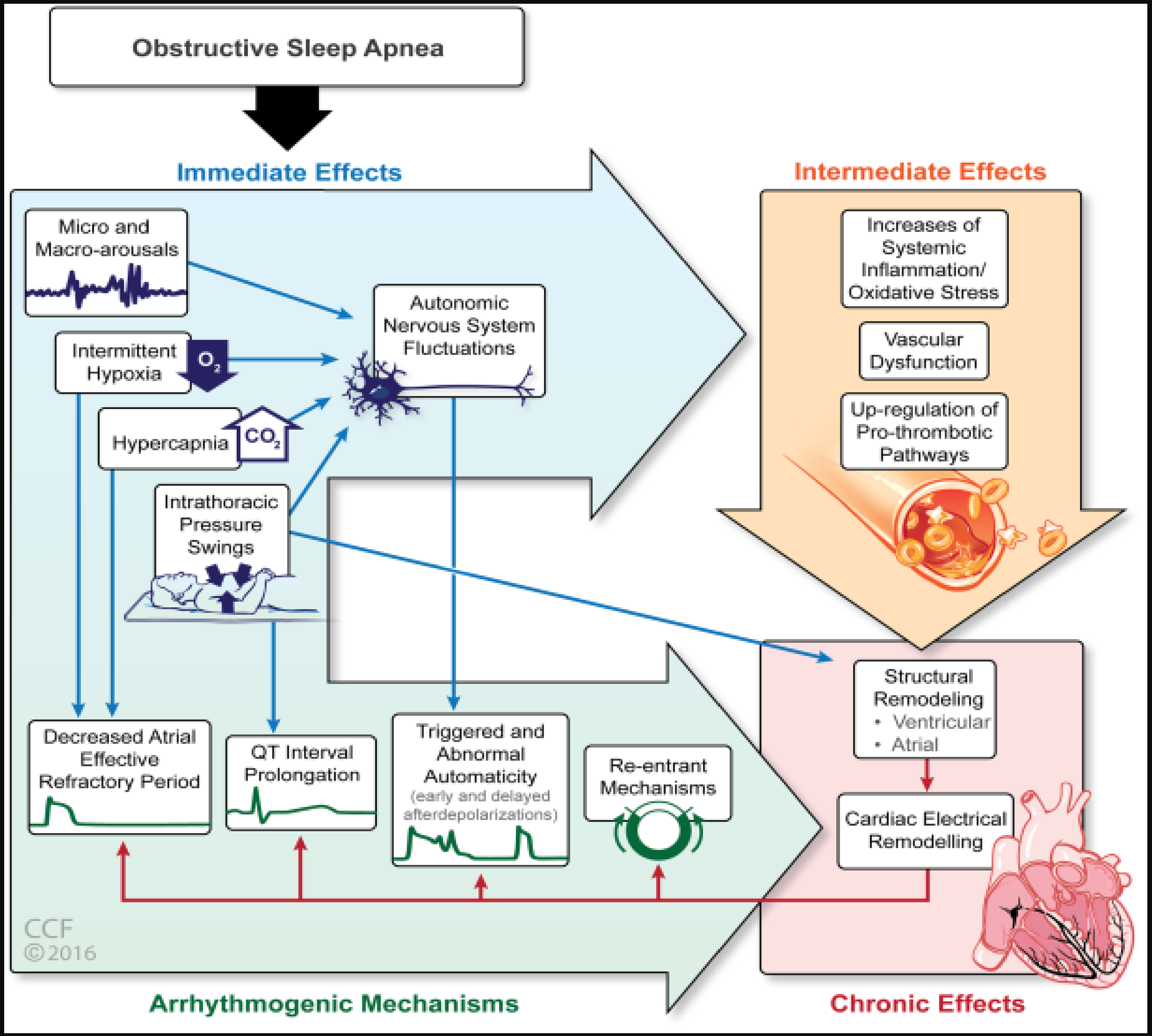
Young T AJRCCM 2002

AF Prevalence and Age



Go JAMA 2001

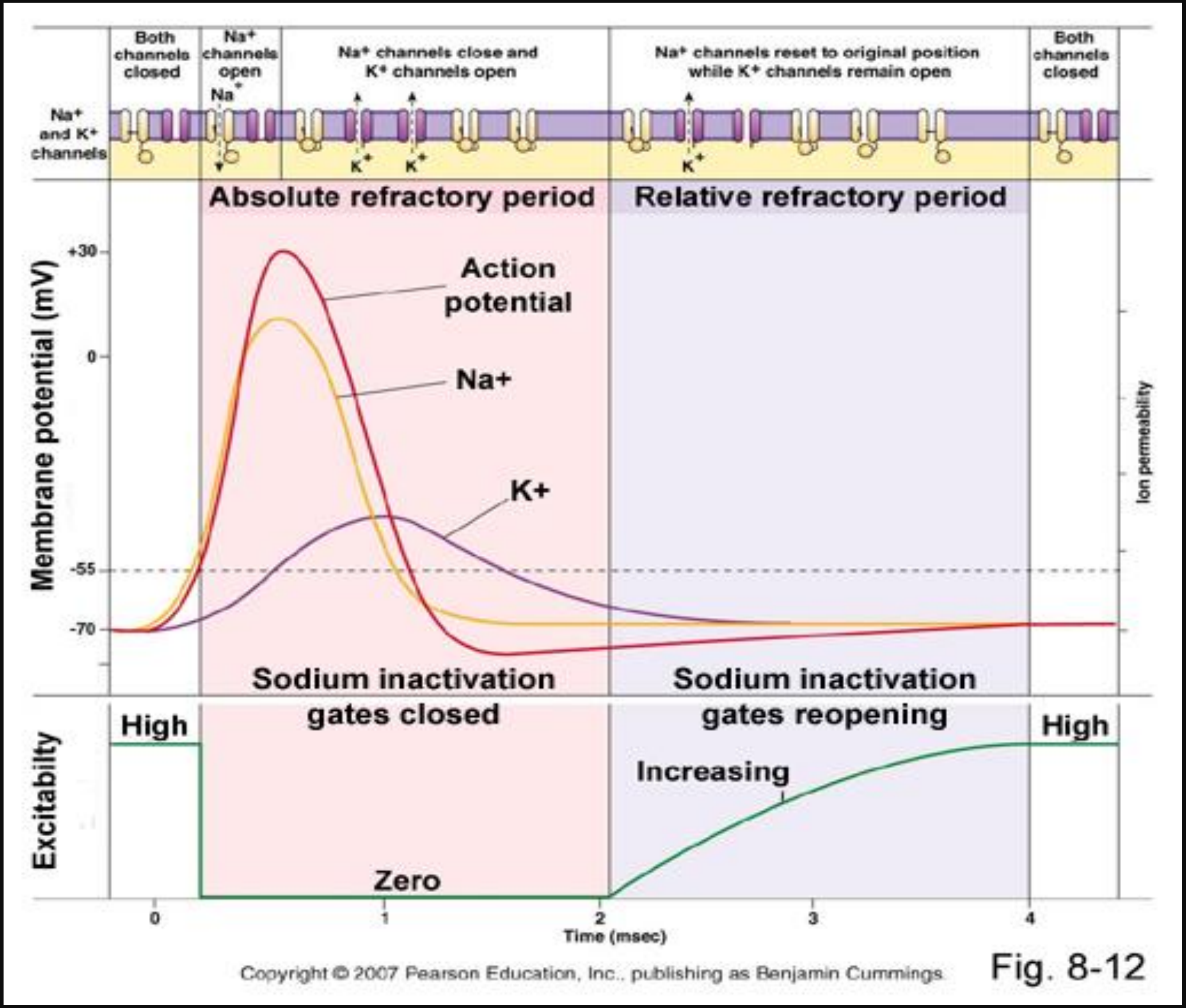
Putative Obstructive Sleep Apnea and Cardiac Arrhythmia Pathophysiologic Pathways



May A, Van Wagoner D, Mehra R. CHEST 2016 Sep 29.

Atrial Fibrillation Inducibility

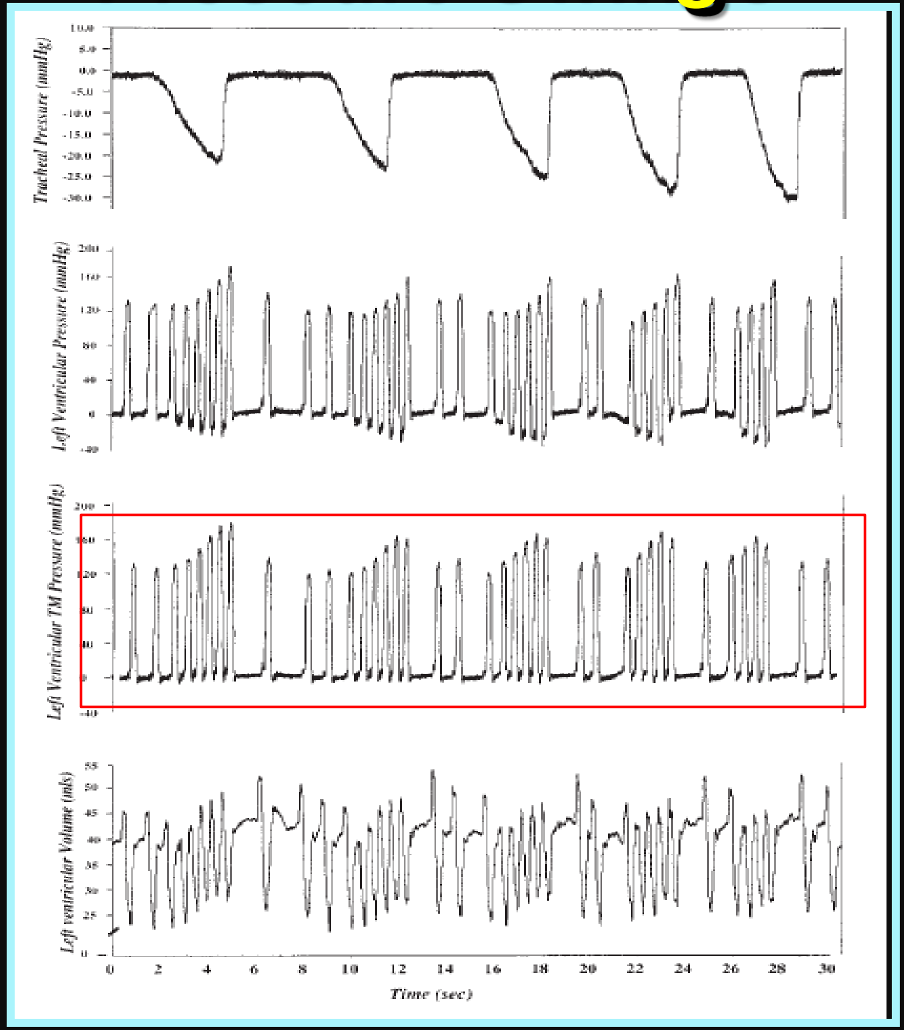
- **Effective or absolute refractory period is the period during which cells cannot be depolarized again**
- **AERP is a period of relative immunity during which cells cannot be excited**



Upper Airway Occlusion Leads to Negative Intrathoracic Pressure Swings

- •Increased preload
- •Increased LV afterload (increased transmural pressure)
- •Impaired diastolic function
- •Atrial and aortic enlargement

Change in atrial volume → AF



Tracheal Pressure (mmHg)

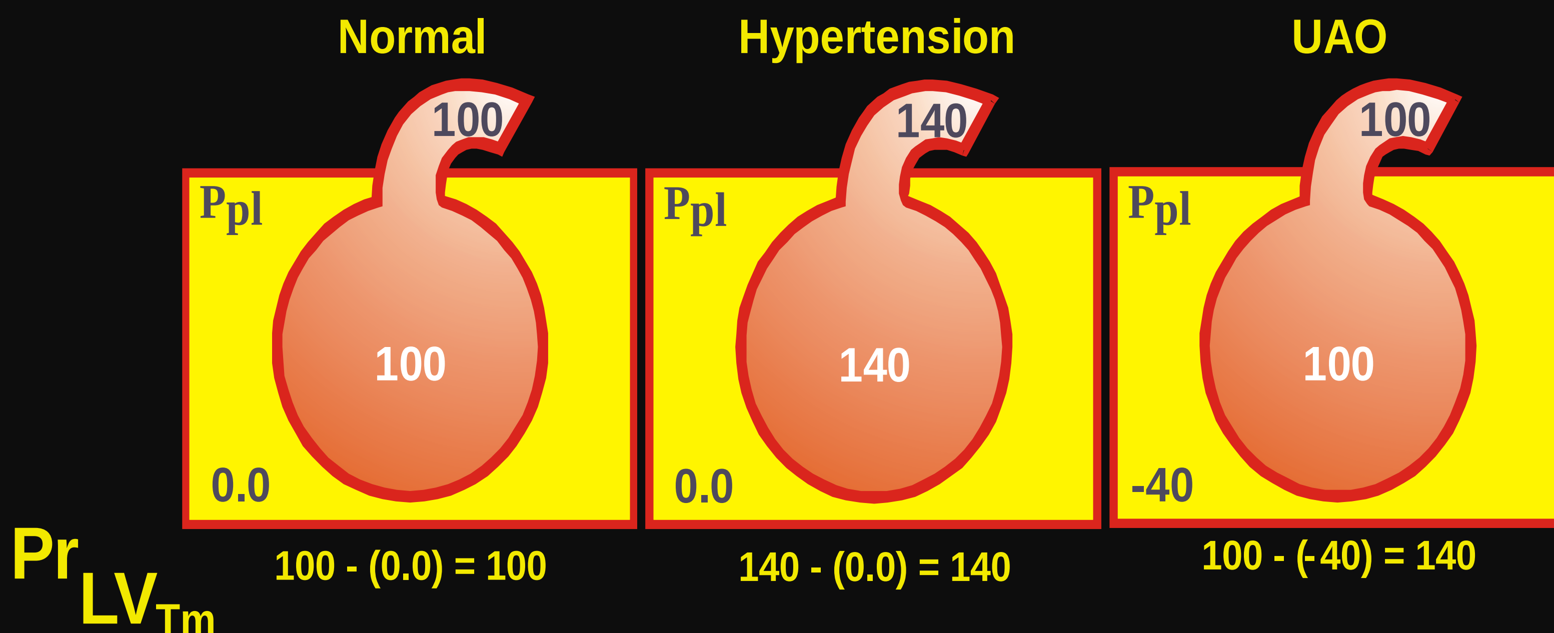
LV Pressure (mmHg)

LV Transmural Pressure (mmHg)

LV End Systolic Volume (mL)

Parker Am J Respir Crit Care Med 1999; 160: 1888-96

Upper Airway Obstruction
↑ LV Transmural Pressure of all Cardiac Chambers



Implications for AF and increase ventricular afterload

Autonomic Blockade Prevents Apnea-Induced AF

- Canine model
- Ablation of the Right PA ganglionated plexus
- Pacing algorithm at 2 min of apnea failed to induce AF

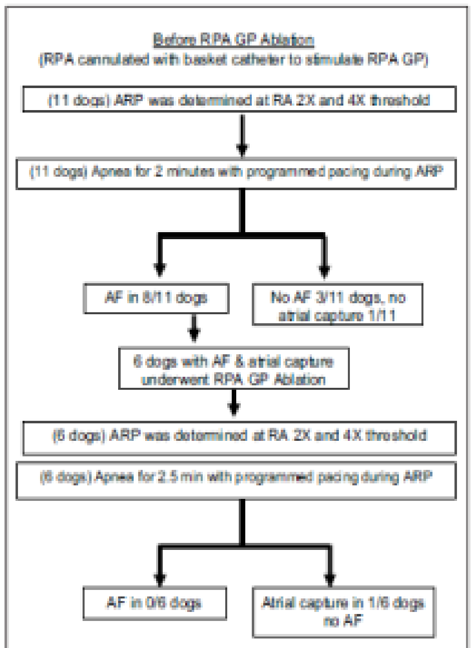


Figure 4 Protocol 2 Flow Chart

In 11 anesthetized dogs, induced apnea was performed before and after the right pulmonary artery (RPA) GP was ablated. Abbreviations as in Figures 1 and 3.

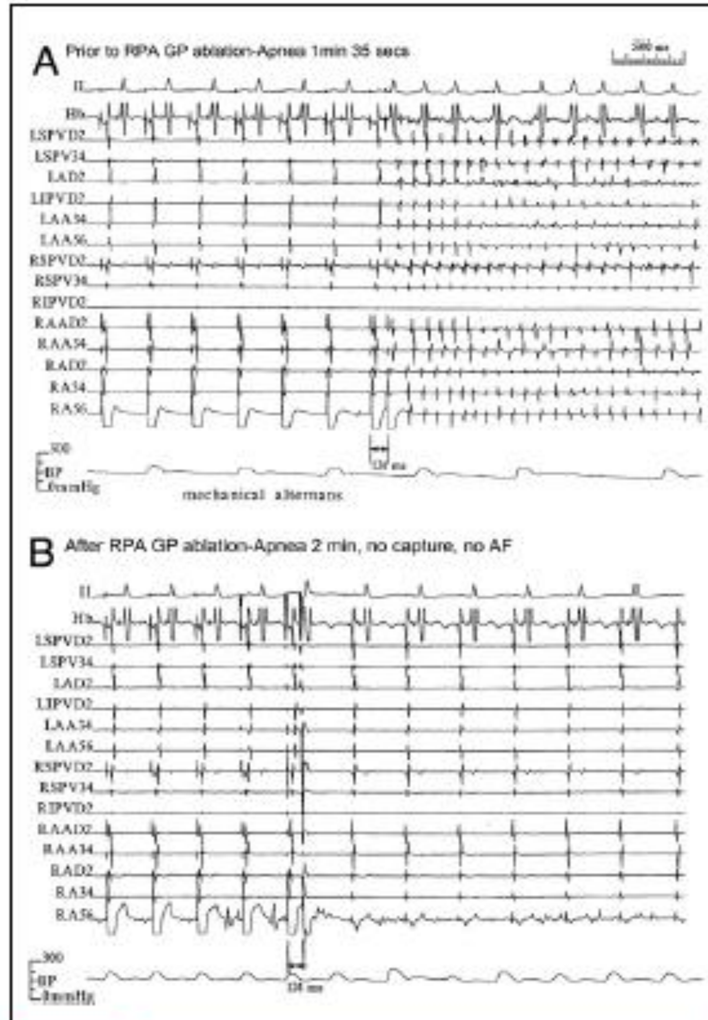


Figure 8 Effect of RPA GP Ablation on AF Inducibility

Ghias M JACC 2009: 54; 22

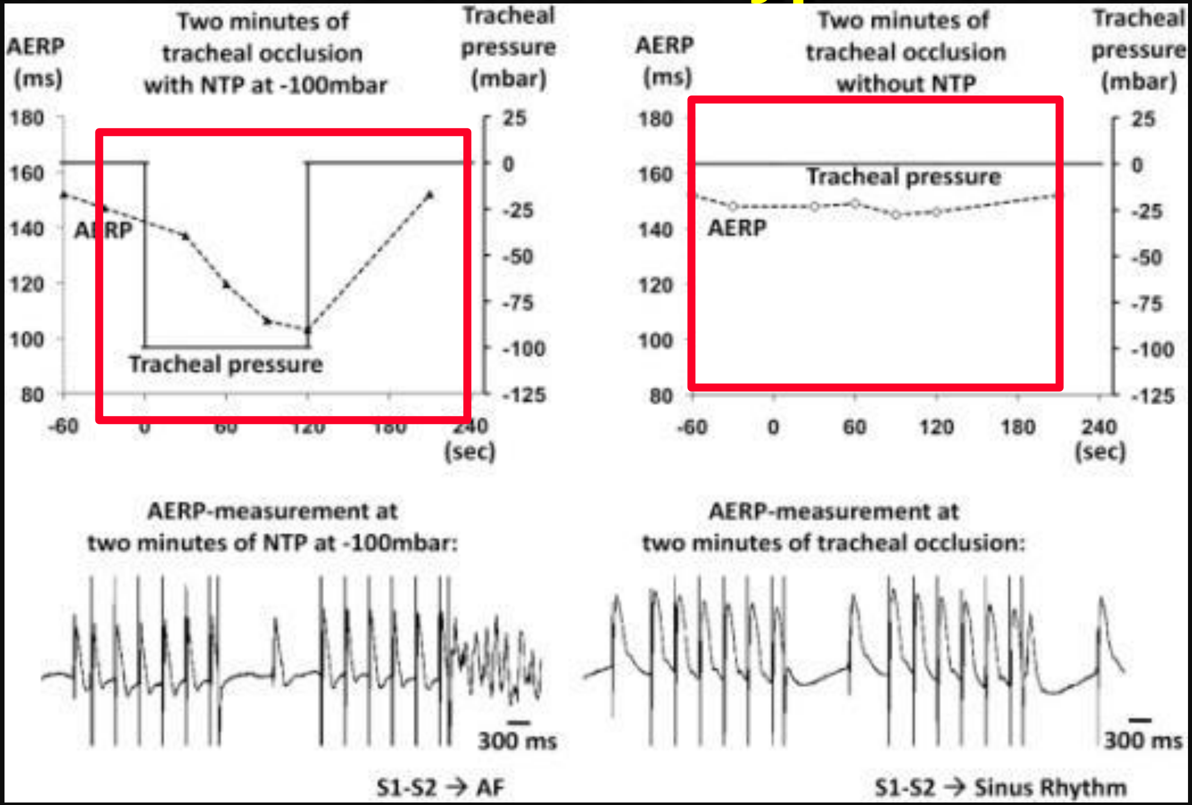
Autonomic Imbalance in OSA and Effects on Refractory Period

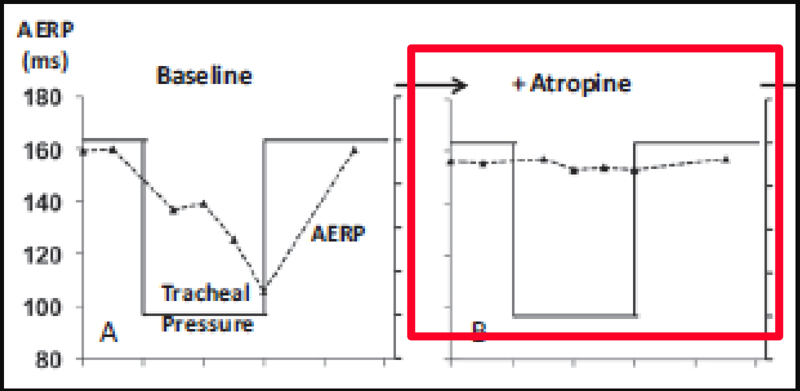
- Post-apneic BP rise inhibited by Renal Sympathetic Denervation
- Renal denervation
  - Anti-arrhythmic effects by mitigating negative tracheal pressure-induced AERP shortening
- Highlights importance of autonomic imbalance in <u>obstructive</u> sleep apnea-associated AF

Linz D Hypertension 2012

Enhanced AF Inducibility in Response to Applied Negative Tracheal Pressure and not Hypoxia Alone

- Progressive shortening of AERP during tracheal occlusion
- Occurred via vagal activation
- Reduced AERP not observed without NTP





Linz D et al Heart Rhythm 2011

Upper Airway Occlusion Leads to:

- Increased Left Atrial Diameter/ Volume
- Reduced Left Atrial Ejection Fraction

Basic Res Cardiol (2014) 109:427
DOI 10.1007/s00395-014-0427-8

ORIGINAL CONTRIBUTION

Chronic obstructive sleep apnea causes atrial remodeling in canines: mechanisms and implications

Jing Zhao · Wei Xu · Fengxiang Yun · Hongwei Zhao · Wenpeng Li · Yongtai Gong · Yue Yuan · Sen Yan · Song Zhang · Xue Ding · Dingyu Wang · Chaowei Zhang · Deli Dong · Chunhong Xiu · Ning Yang · Lei Liu · Jingyi Xue · Yue Li

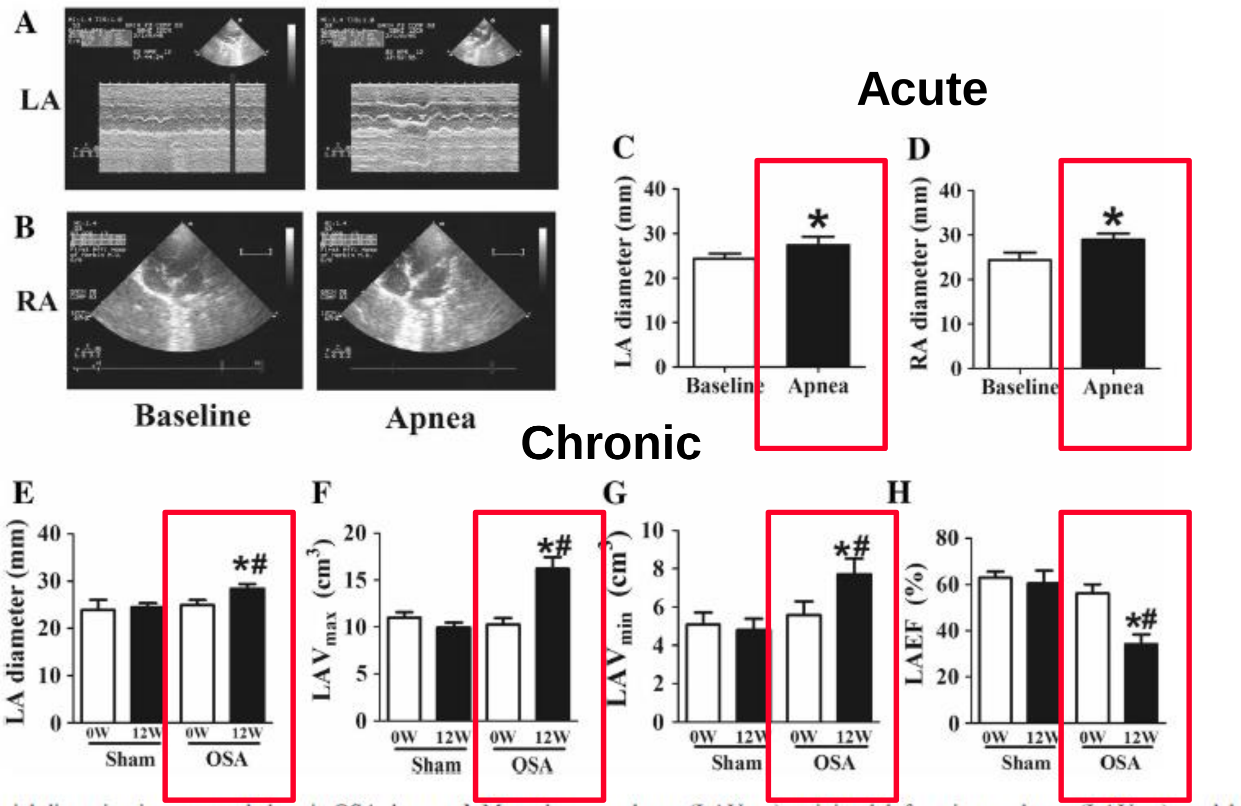


Fig. 3 Atrial distention in acute and chronic OSA dogs. **a**, **b** M-mode images showing changes in LA and RA dimensions in baseline and after acute apnea. **c**, **d** Quantification of LA and RA diameter changes in baseline and after acute apnea. *$P < 0.05$ vs. baseline, $n = 5$ each group. **e–h** Left atrial dimension (LAD), maximum left atrium volume (LAV_{max}), minimal left atrium volume (LAV_{min}), and left atrium ejection fraction (LAEF) in sham and chronic OSA dogs. *$P < 0.05$ compared with 0 week in OSA group; $^{\#}P < 0.05$ vs. 12 weeks of sham group, $n = 4$ each group

Sleep Apnea and Cardiac Morphology

- Increased LVM and LVH (Sleep Heart Health Study)
  - Adjusted LVMI 7% higher in AHI > 5 versus <5
    - 41.4 vs 44.1 $g/m^{2.7}$
  - Stronger associations of LVMI with hypoxemia indices vs AHI
  - LVH: OR 1.78 (1.14, 2.79)
    - Increased LVIDd
    - Eccentric Hypertrophy

Chami H Circulation 117: 2599. 2008

- Impaired LV Diastolic Function

Arias MA Circulation 2005: 112: 375, Kim SH AJC 2008: 101: 1663; Oliveira JASE 2008: 21: 1355

  - Improved E/A, IVRT, mitral DT with CPAP versus sham CPAP

Arias MA Circulation 2005: 112: 375

- Increased Left Atrial Size
  - Associated with AHI severity and E/E’ ratio

Oliveira W JASE 2008: 21: 1355

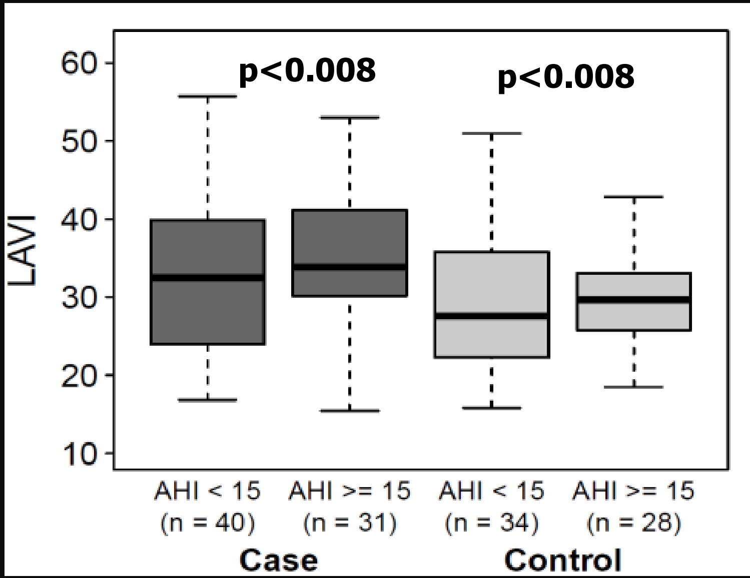
  - Associated with arterial stiffness (pulse wave velocity)

Drager LF Int J Cardiol. 2010: 144: 2

Left Atrial Echocardiographic Parameters in Sleep Disordered Breathing and Paroxysmal Atrial Fibrillation

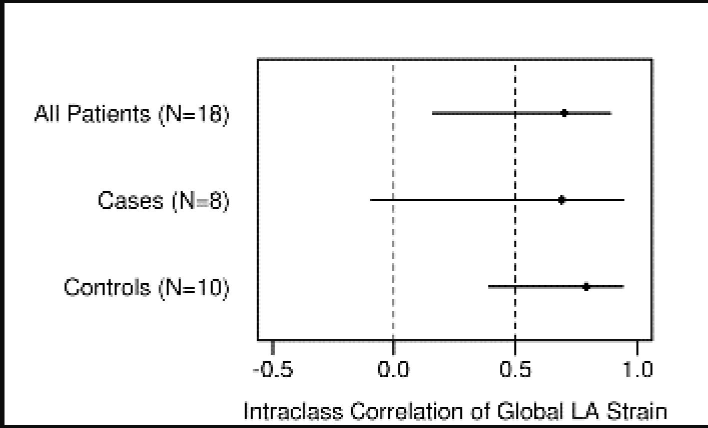
- Prior work has not examined LA indices in AF; specifically not in paroxysmal AF
- n=154 participants
  - n=78 PAF
  - n=80 controls
- LA volume index (indexed for body surface area) increased in PAF and controls

- LA strain: utility in predicting sinus rhythm maintenance after AF ablation
- Limited data on reliability of LA strain data in PAF
- In n=18 participants
  - LA strain reliability in PAF (n=8) was *good*: ICC=0.69, 95% CI:0.09 – 0.94
  - LA strain reliability in controls (n=10) was *excellent* (ICC=0.79, 95% CI: 0.39 – 0.94)



Sushruta Duara Cerejo MD

Duara Cerejo et al SLEEP 2016 NIRD research day award



Bo Xu MBBS FRCP Cardiac Imaging

Xu B et al World Congress on Heart Disease 2017 Platform presentation

Hypoxia Results in Abnormal Automaticity and Triggered Activity

Prolonged mild hypoxia and acidosis in guinea pig ventricular myocardium led to delayed after depolarizations and triggered activity

Under conditions that mimic ischemia/ hypoxia, abnormal automaticity and triggered activity occurred in dog pulmonary vein sleeves

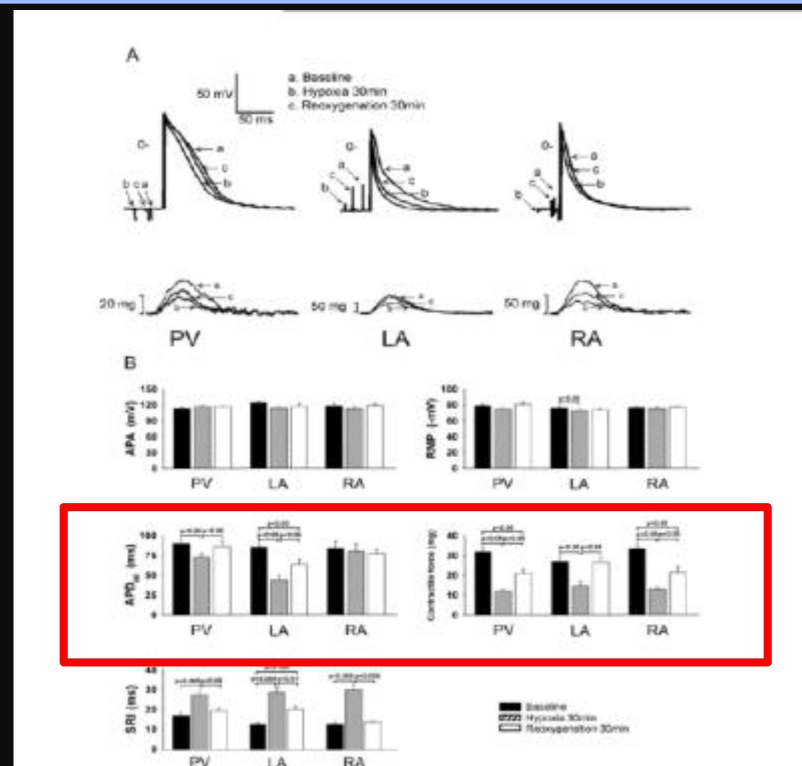
Adamantidis MM, 1985
Wang T, et al. International Journal of Cardiology 104 (2005) 59-66

Clinical Science (2012) **122**, 121–132 (Printed in Great Britain) doi:10.1042/CS20110178

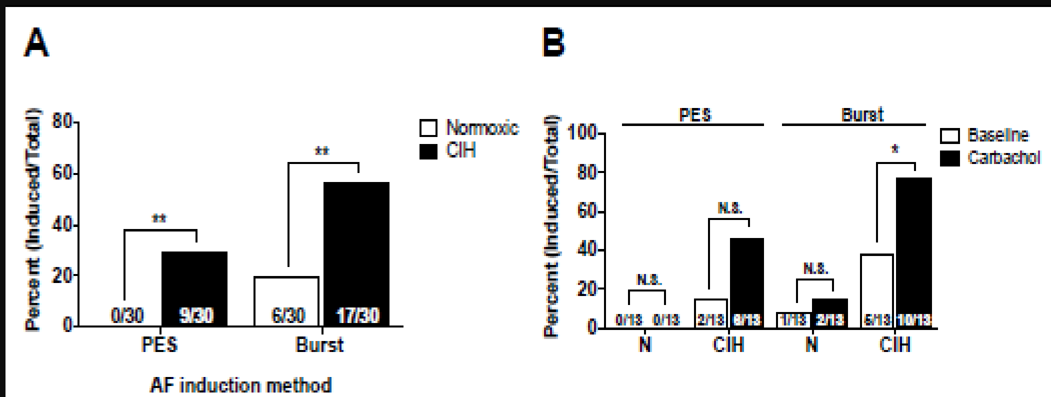
Hypoxia and reoxygenation modulate the arrhythmogenic activity of the pulmonary vein and atrium

Hypoxia reduced AP duration in LA and PV

Reoxygenation reversed hypoxic effects but induced PV burst firings



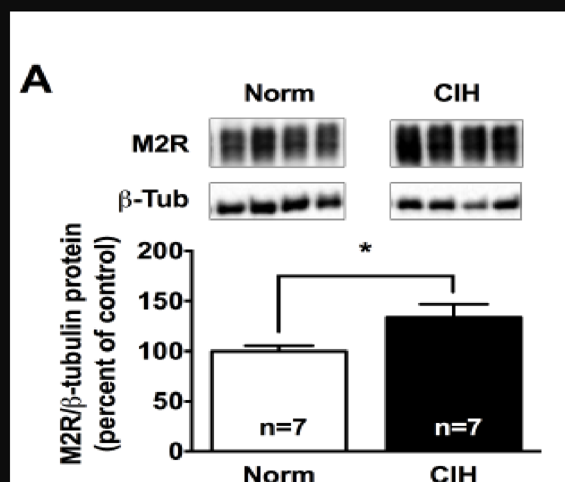
Chronic Intermittent Hypoxia in Rats Leads to Atrial Arrhythmia

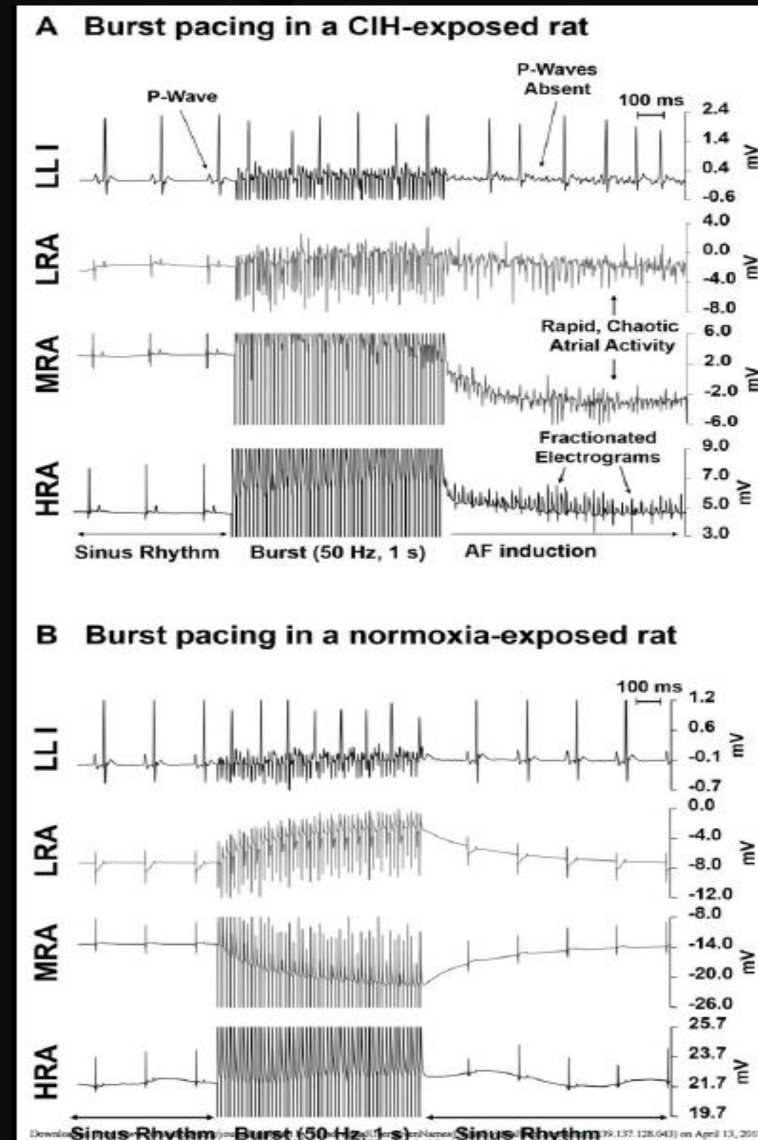


CIH: Enhanced AF vulnerability using PES and burst pacing

Accentuated by carbachol and abolished by atropine

Higher M2 receptor protein levels



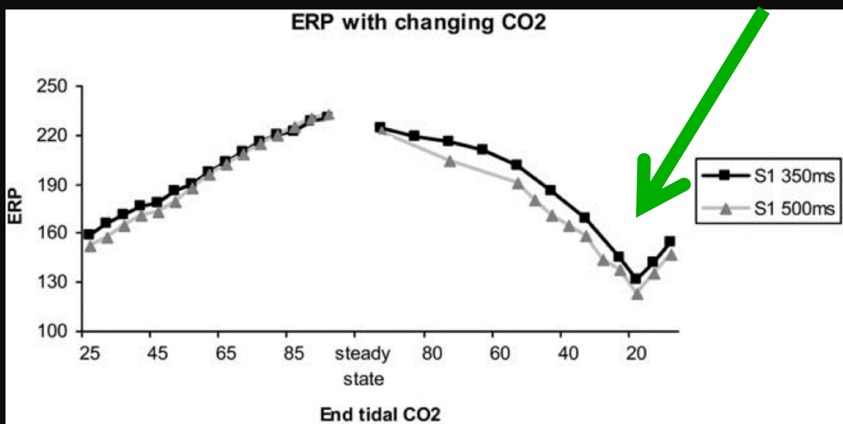


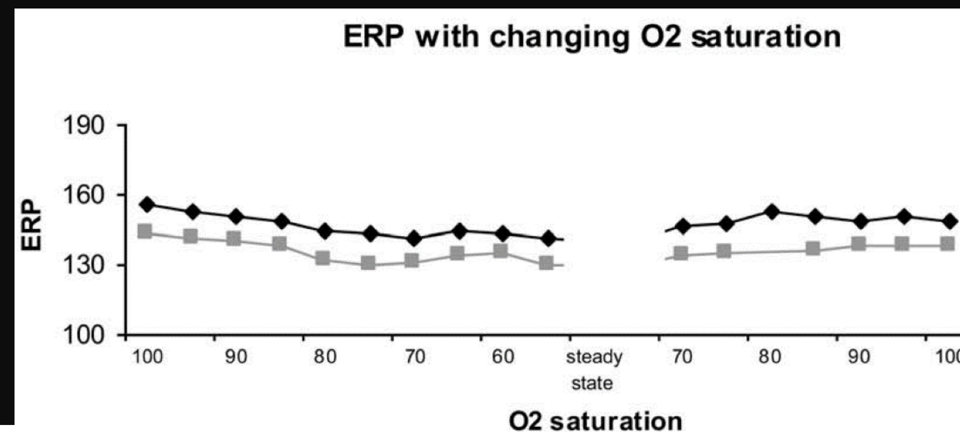
Bober SL, et al. m J Physiol Heart Circ Physiol. 2018 Feb 9.

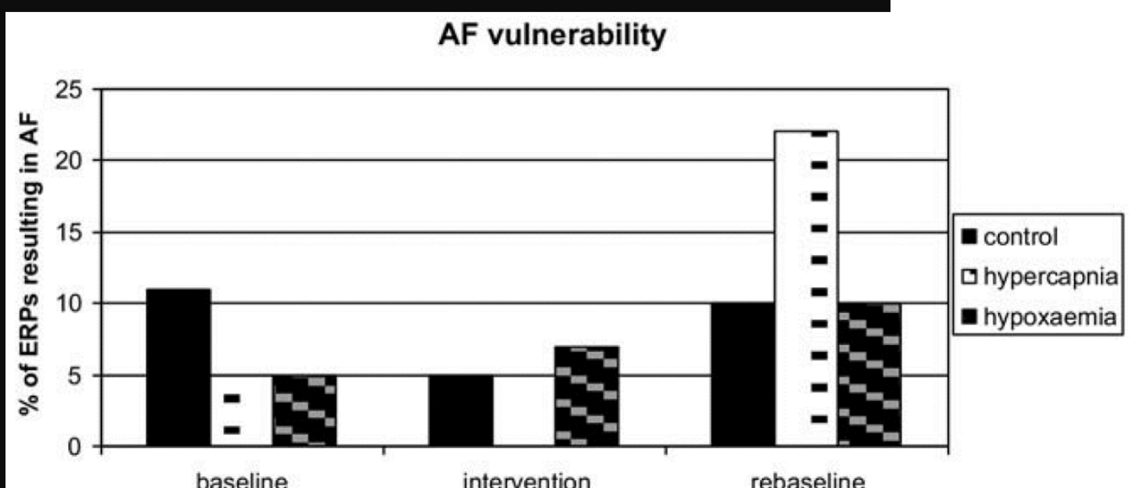
Electrophysiologic Effects of Hypercapnia

17 sheep – 6 control, 5 hypercapnia, 6 hypoxemia

Linear step-wise changes in the Atrial ERP with induction and resolution of hypercapnia







AF vulnerability increased significantly with return to eucapnia (when ERP overshot and shortened, but conduction time remained prolonged)

Stevenson IH, et al Heart Rhythm 2010; 7:1263-70

Intersecting Pathways of Systemic Inflammation and Oxidative Stress

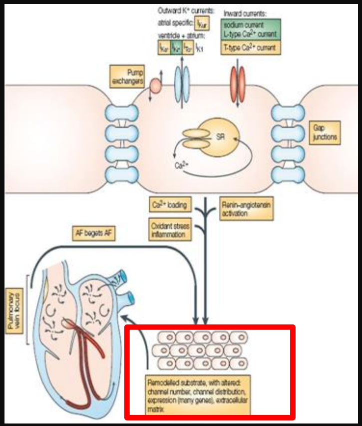
- **Sleep Apnea**
  - Upregulation of inflammatory mediators
    - IL6, sIL6R*, IL-8, TNFα, CRP (NF-Kappa B)

      Yokoe T Circulation 2003: 107: 8, Mehra Arch IM 2009
  - Enhanced thrombotic potential
    - PAI-1*, fibrinogen*, P-selectin
    - VEGF

      Mehra R AJRCCM 2010, Lavie L AJRCCM 2002: 165
  - Oxidation of serum proteins and lipids
- **Atrial Fibrillation**
  - Oxidative stress
    - Myeloperoxidase related to early AF recurrence

      Richter B Clin Res Cardiol 2012: 101: 3
  - IL-6 and CRP
    - Correlate to longer AF duration, AF development and recurrence and thrombogenesis

      Issac TT J Am Coll Cardiol 2007: 50



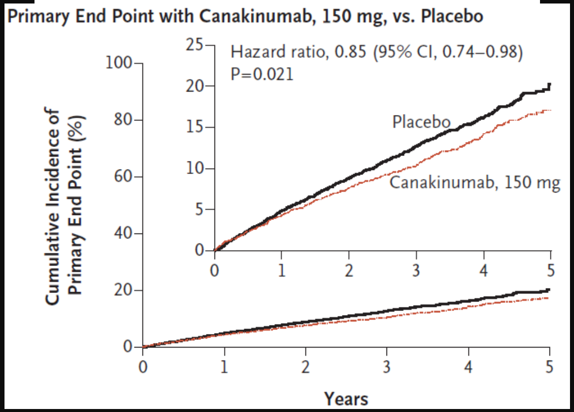
Viswanathan MN Albert Einstein College of Medicine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

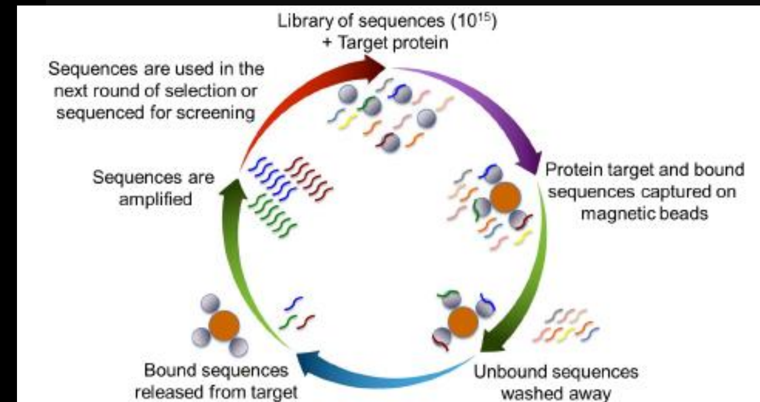
P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

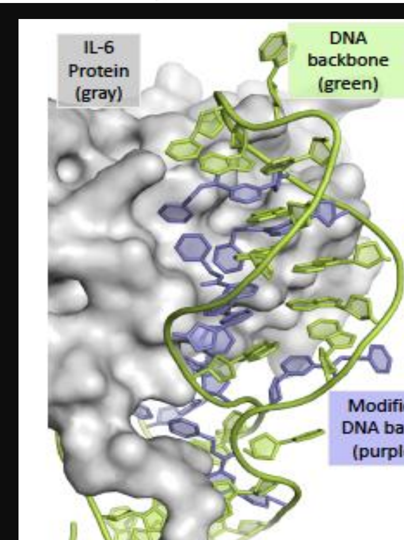


CANTOS RCT- targeted IL-1 beta, n=10K

Proteomics Approach in Atrial Fibrillation and Sleep Apnea

- Understand biology and develop predictive signature profiles
- Highly multiplexed aptamer-based proteomic technology for unbiased examination and quantification of plasma protein biomarkers (SOMAscan, SomaLogic, Inc, Boulder, CO)
- Aptamers are single stranded nucleic acids selected to tightly bind to a specific target molecule
- Simultaneously quantified 1310 proteins in a plasma sample (<100 uL)
- Median lower limit of quantitation of 0.3 pM, dynamic range of 0.5 logs



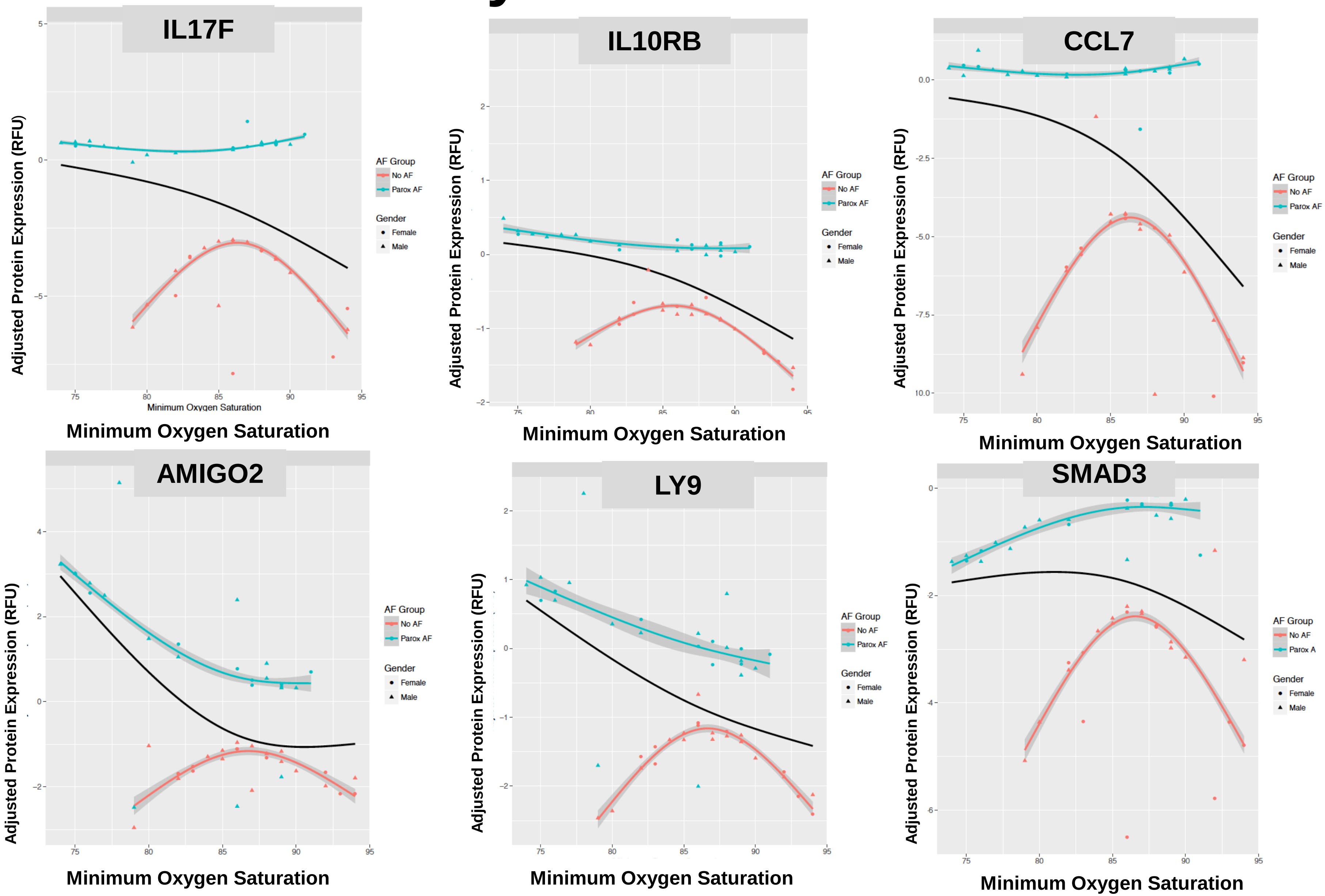


an et al. © Somalogic, Inc

Keeney TR et al. Automation of the SomaLogic Proteomics Assay: A Platform for Biomarker Discovery. Journal of The Association for Laboratory Automation

Ganz et al JAMA. Development and Validation of a Protein-Based Risk Score for Cardiovascular Outcomes Among Patients With Stable Coronary Heart Disease2016;315(23):2532-2541.

Hypoxia and Protein Biomarkers by Paroxysmal AF Status



Proteomics Approach in Atrial Fibrillation and Sleep Apnea

- In this middle-aged, obese, predominantly male sample case control study, we identified themes of altered proteomic signature profiles in paroxysmal AF and interactions with sleep apnea indices

- In those with paroxysmal AF versus controls, alterations in protein profiles was observed:
  - Chemokines, CCL13, CCL28, CCL7
  - Interleukins, IL10RB, IL17F
  - Phospholipases, PLA2G2A, PLA2G2E
  - Markers of fibrosis, MBL2, SMAD3, SNAP25

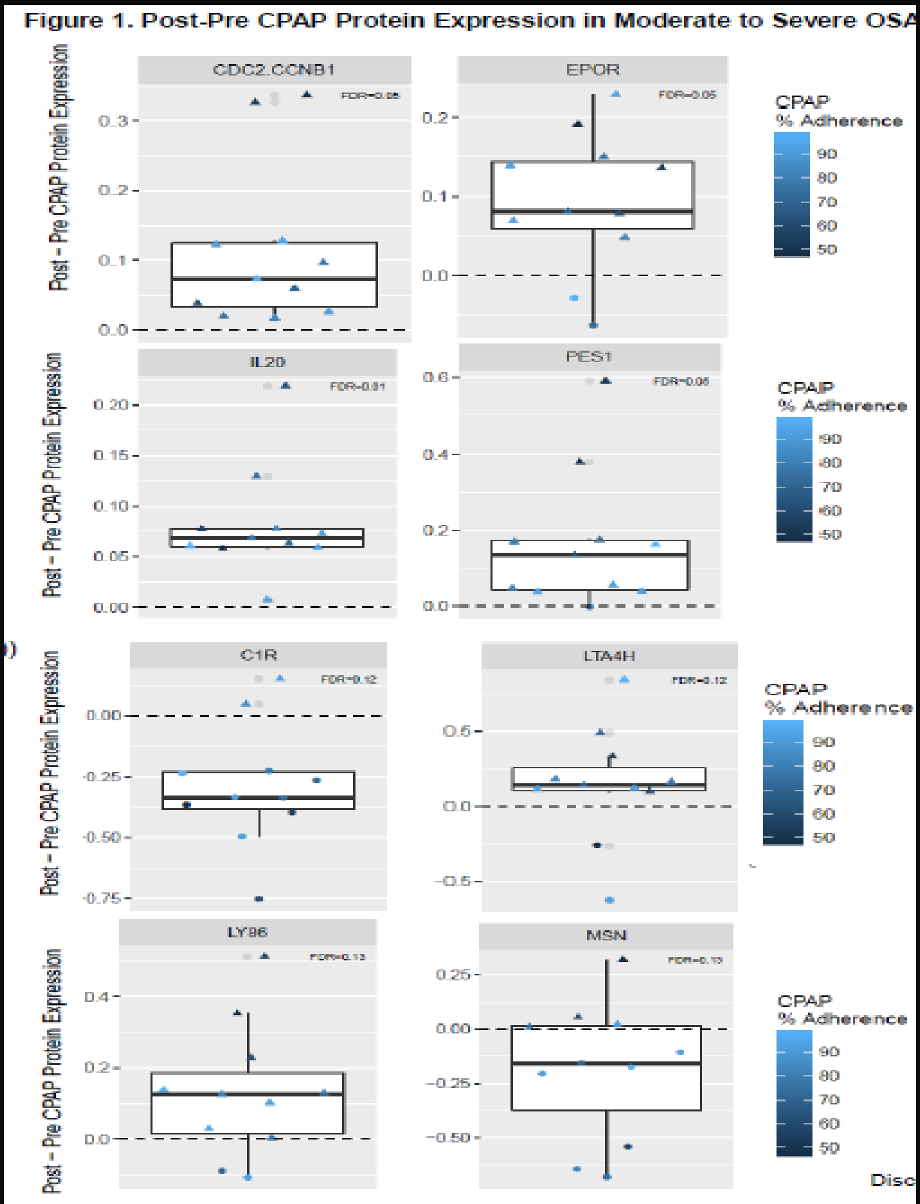
Mehra R, Barnard J, Van Wagoner D. American Thoracic Society platform presentation, 2017

Proteomics Approach in Atrial Fibrillation and Sleep Apnea

- Differential association of increasing **hypoxia (nadir SaO2)** in those with paroxysmal AF versus controls in the following (some identified in paroxysmal AF vs control analysis highlighted):
  - Interleukins, IL10RB, IL17F
  - Chemokines, CCL7
  - Markers of fibrosis, SMAD3
  - Endothelial apoptosis, AMIGO2
  - Lymphocyte activation, LY9
- Differential association of increasing **OSA category (defined by AHI)** in those with paroxysmal AF versus controls in the following (some identified in paroxysmal AF vs control analysis highlighted):
  - Interleukins, IL10RB, IL17F
  - Chemokines, CCL7
  - Lymphocyte activation, LY9
  - Interferon, IFNG

Mehra R, Barnard J, Van Wagoner D. American Thoracic Society platform presentation, 2017

Alterations of Proteomic Signatures with CPAP use in Paroxysmal AF

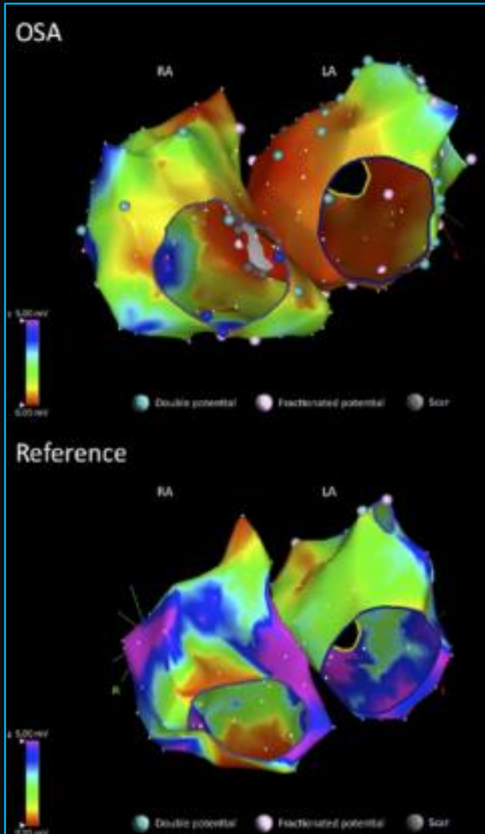


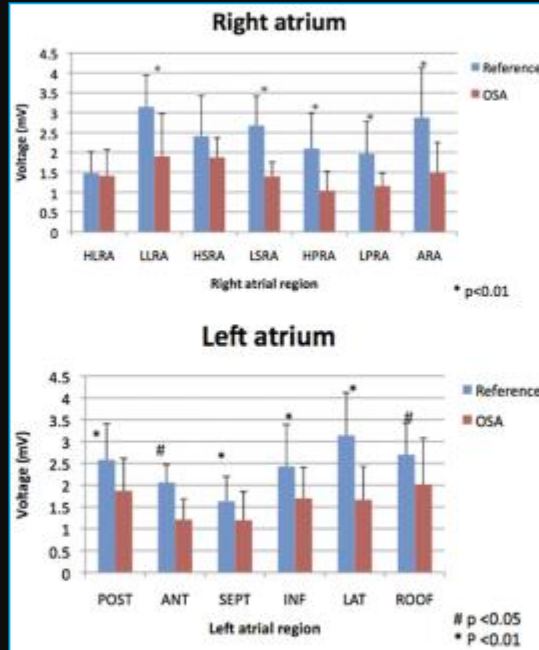
- CPAP-treatment related improvements in biologically plausible circulating biomarkers:
  - systemic inflammation
  - vascular remodeling proteins
  - Markers of fibrosis and thrombosis

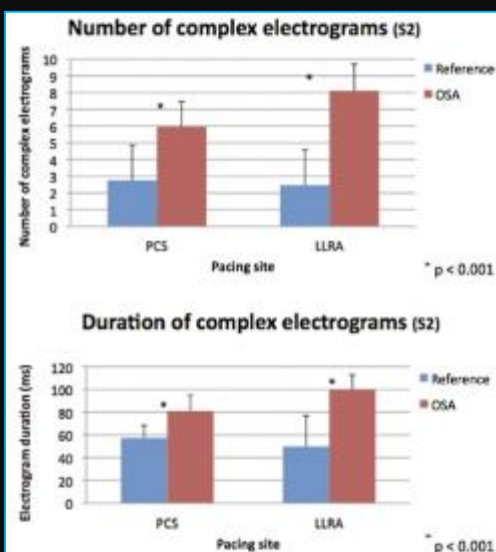
  in response to OSA treatment with CPAP in paroxysmal AF
- Preliminary findings require independent verification via replication and validation studies

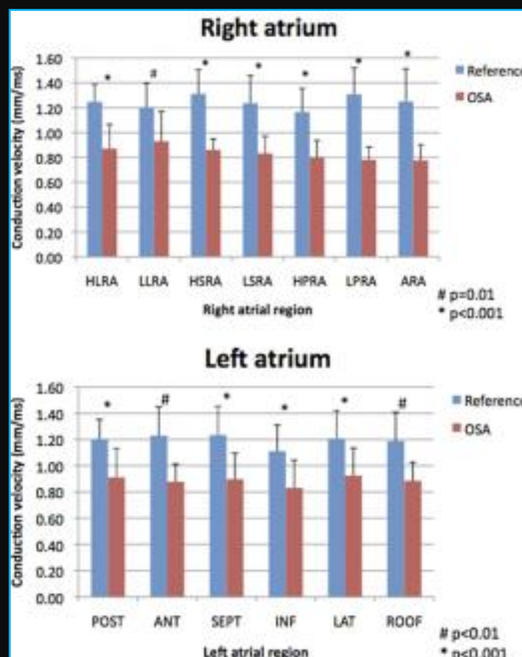
Mehra R, Barnard J, Van Wagoner D. ATS 2017

Structural and Electrical Remodeling in OSA









40 pts in SR with, 20 without OSA undergoing AF catheter ablation for PAF

- **Structural remodeling**
  - Electroanatomic voltage map
  - ↑d L and R atrial size
- **Electrical remodeling**
  - Lower atrial voltage
  - ↑Complex fractionated electrograms (CFAE)
  - ↓Conduction velocity

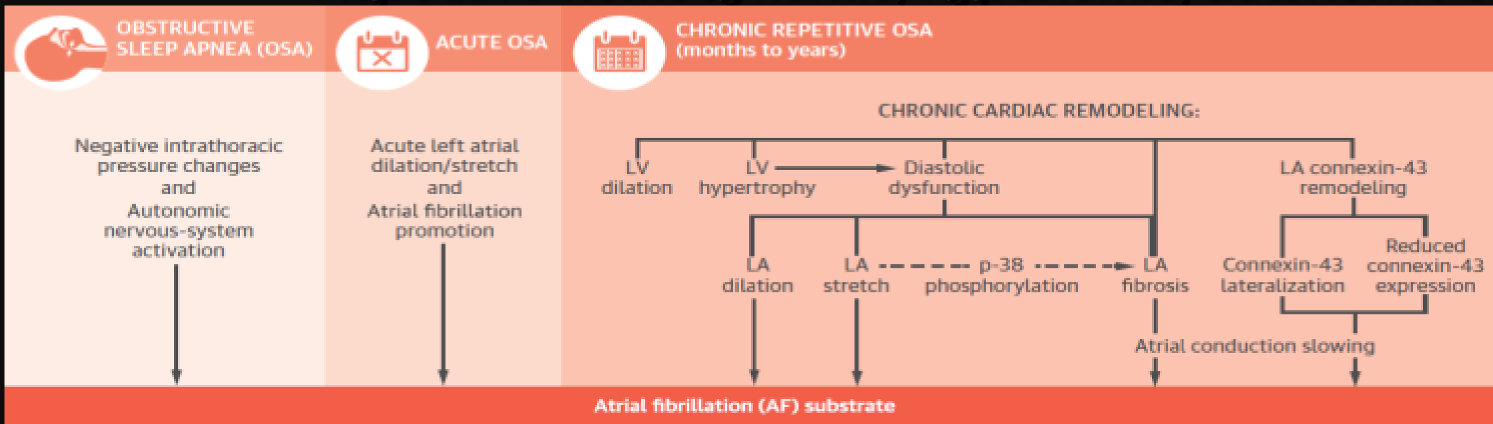
Extensive areas of low voltage and electrical silence suggestive fibrosis or conduction dissociation

- **Substrates for atrial reentrant arrhythmias**

Dmitri H, et al Heart Rhythm 2012; 9:321–327

Altered AF Substrate in Apnea-Induced AF

Repetitive hemodynamic, hypoxemic, autonomic surges



Iwasaki YK, et al. JACC 2014; 64:2013-23

Structural Remodeling

- ↑LA size ⇒ promotes propagation of AF
- ↑LV mass, LVH, RV thickness ⇒ diastolic dysfunction, HFpEF

Inflammation
Oxidative Stress
Atrial stretch

Electrical remodeling

- ↓Atrial conduction velocity
  - Connexin remodeling
  - Fibrosis
    - Atrial stretch- and catecholamine-mediated channels
      - DADs, focal PV discharges
- ↓Atrial refractoriness
  - ↓A ERP at PV ostia
  - ↓Atrial ERP

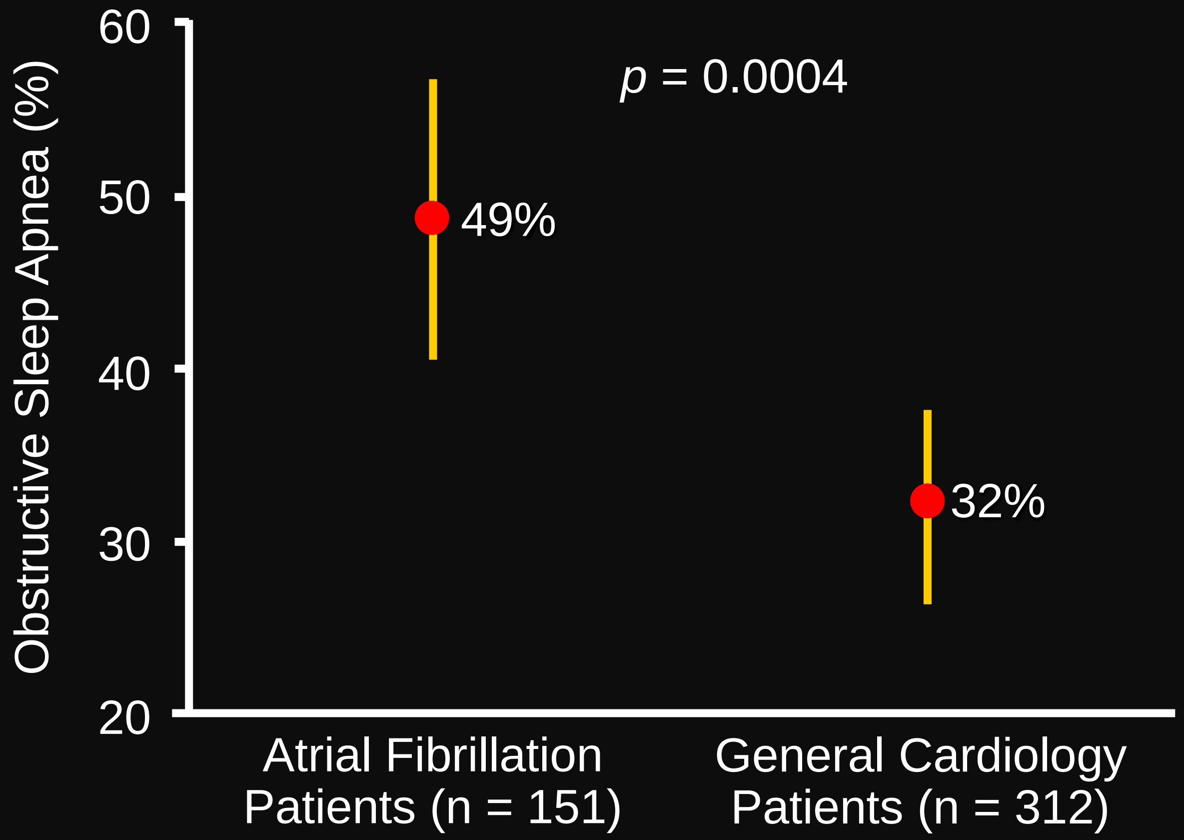
AF

Autonomic Nervous System

- Vagal stimulation
  - ↓ Atrial ERP
  - ↓ Refractoriness at PV ostia
- Sympathetic Surges
  - Triggered after-depolarizations

Sleep Apnea and Atrial Fibrillation
Prevalence

Results: % of patients with OSA

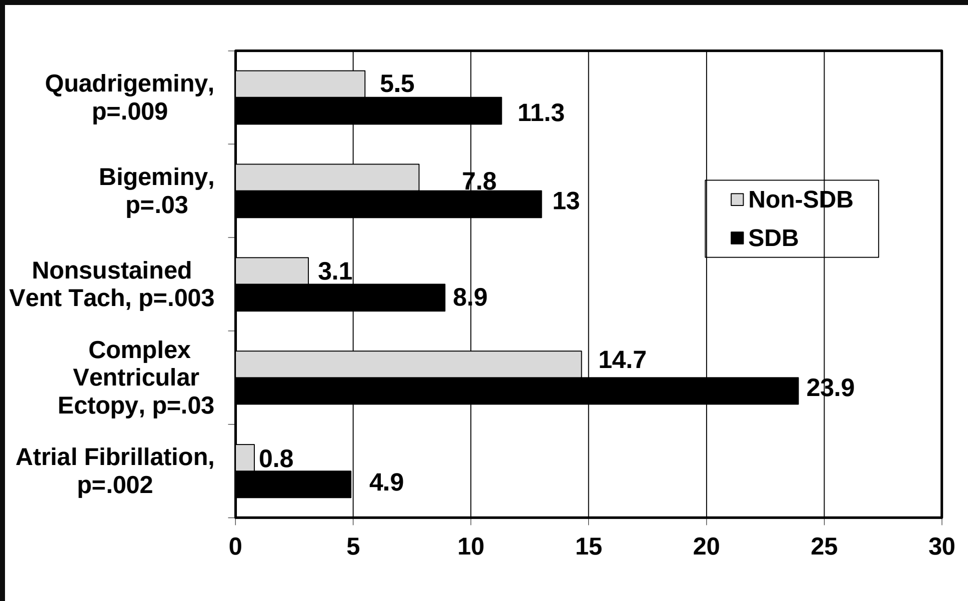


Gami *Circulation*. 2004; 110; 364

Prevalence of Nocturnal Cardiac Arrhythmias According to Sleep Disordered Breathing Status

Group-Matched by Age, Sex, Race, BMI

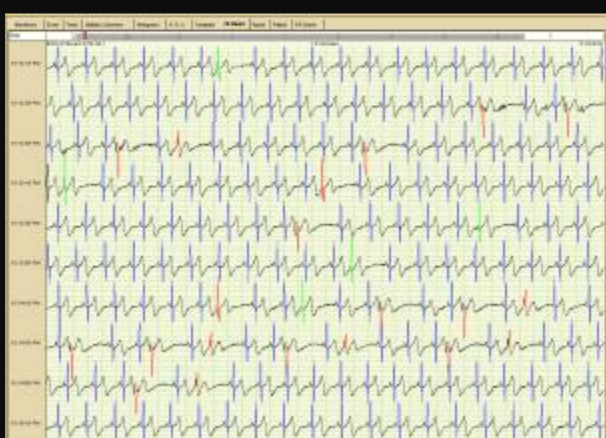
Sleep Heart Health Study

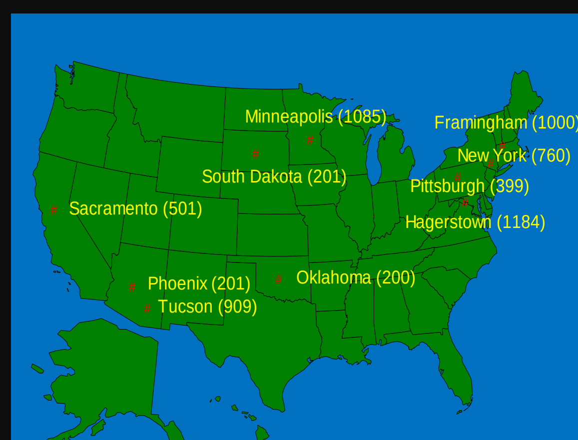


	Adjusted OR	95% CI
Atrial Fibrillation	4.5	1.2, 17
CVE or NSVT	1.8	1.2, 2.8
AF or NSVT	3.7	1.7, 8.0

CVE Odds > 7.0, 50-60 years old

Mehra R at al Am J Respir Crit Care Med 2006



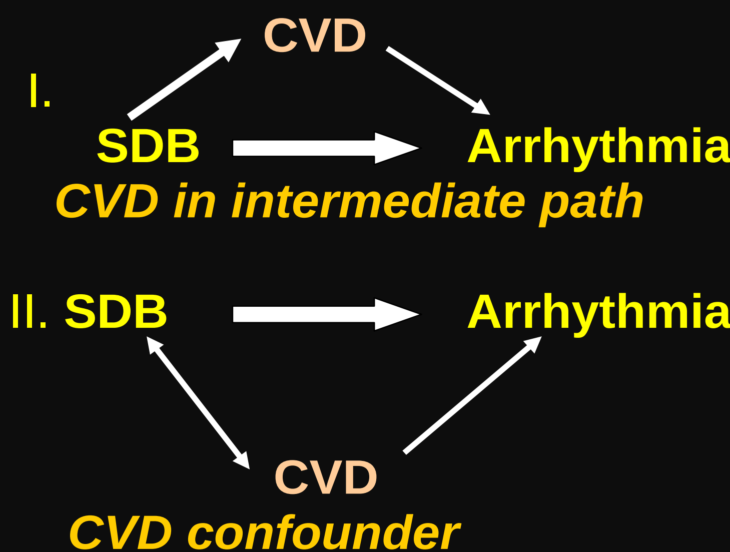


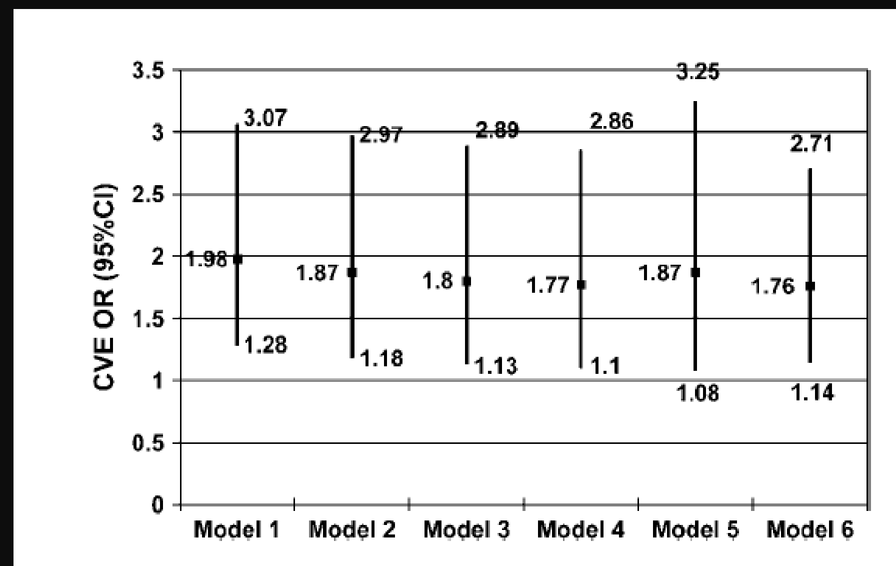
Association of Nocturnal Arrhythmias with Sleep-disordered Breathing
The Sleep Heart Health Study

Reena Mehra, Emelia J. Benjamin, Eyal Shahar, Daniel J. Gottlieb, Rawan Nawabit, H. Lester Kirchner, Jayakumar Sahadevan, and Susan Redline

Departments of Medicine and Pediatrics, Case Western Reserve University, Cleveland, Ohio; Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; and Division of Epidemiology, University of Minnesota, Minneapolis, Minnesota

Is Cardiovascular disease as an Intermediate Factor or a Confounder?





Association of Nocturnal Arrhythmias with Sleep-disordered Breathing

The Sleep Heart Health Study

Reena Mehra, Emelia J. Benjamin, Eyal Shahar, Daniel J. Gottlieb, Rawan Nawabit, H. Lester Kirchner, Jayakumar Sahadevan, and Susan Redline

Departments of Medicine and Pediatrics, Case Western Reserve University, Cleveland, Ohio; Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; and Division of Epidemiology, University of Minnesota, Minneapolis, Minnesota

Statistically significant interaction with SDB and age relative to complex ventricular ectopy.

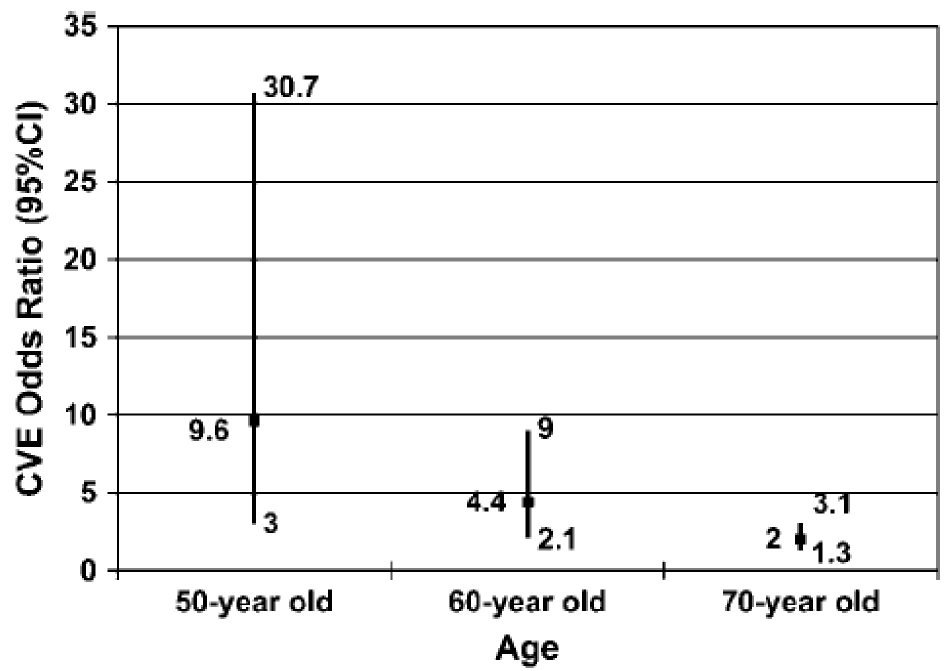
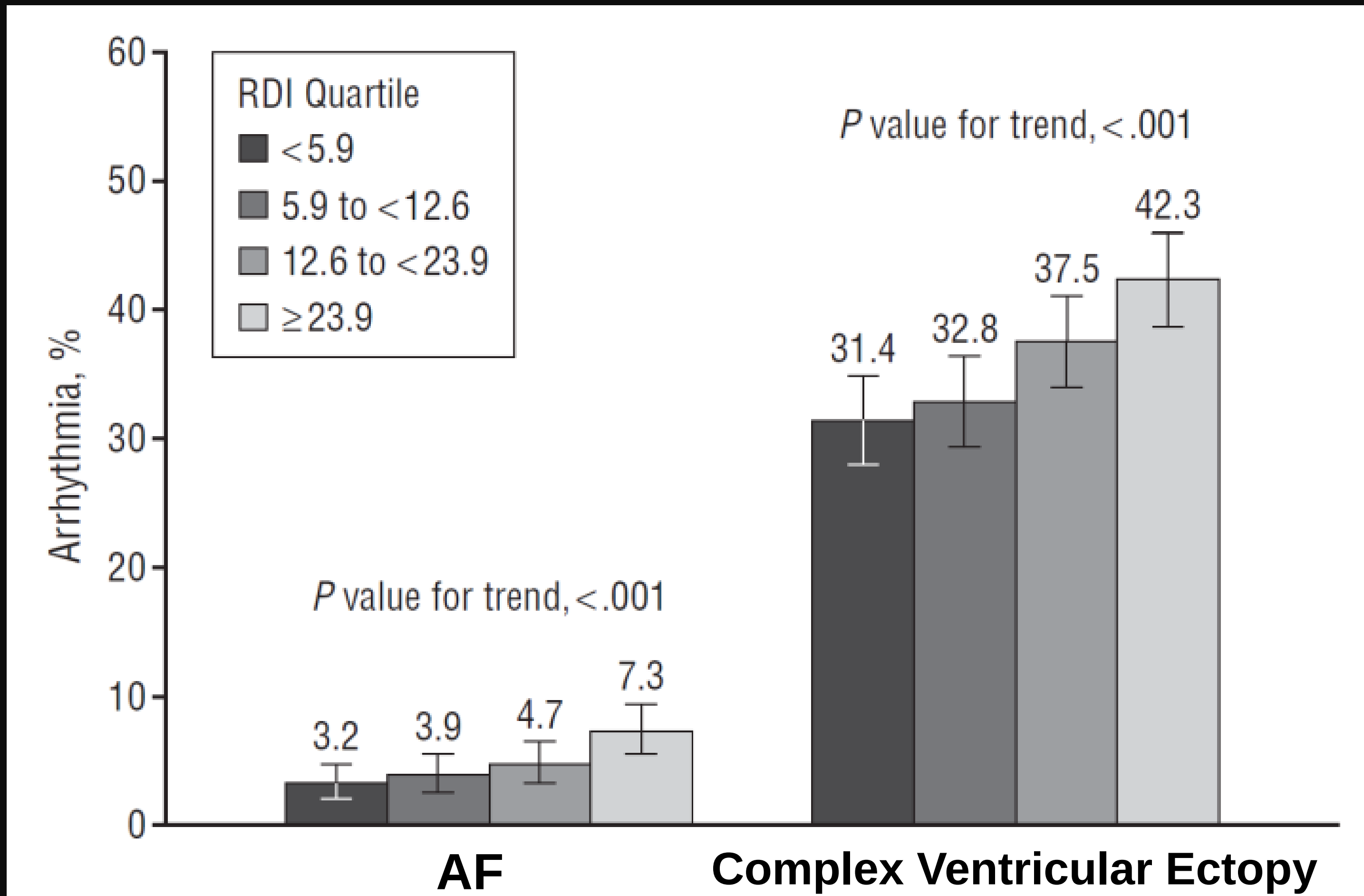


Figure 3. ORs (95% CI) of complex ventricular ectopy in subjects with SDB according to age adjusted for coronary artery disease. This graph depicts the ORs (95% CI) of complex ventricular ectopy adjusted for coronary heart disease according to our final model given a 50-, 60-, and 70-yr-old person, respectively.

Sleep Apnea and Arrhythmia Monotonic Relationships

n=2911

MrOS Sleep Study



Mehra R et al Arch Int Med 2009

RDI = Respiratory Disturbance Index

Sleep Apnea and Atrial Fibrillation

SDB Quartile Odds Ratio (95% CI)	OA Quartile Odds Ratio (95% CI)	CA Category Odds Ratio (95% CI)	CSR-CSA Odds Ratio (95% CI)	Hypoxia Odds Ratio (95% CI)
Reference	Reference	Reference	**4.54 (2.96-6.96)***	Reference
1.38 (0.74-2.57)	1.49 (0.83-2.67)	0.81 (0.49-1.36)		1.33 (0.84-2.12)
1.58 (0.85-2.91)	1.21 (0.66-2.21)	1.05 (0.53-2.05)		1.11 (0.59-2.07)
2.15 (1.19-3.89)*	1.49 (0.83-2.68)	**2.69 (1.61-4.47)***		1.30 (0.71-2.40)

- **Dose response relationships**
- **Moderate to severe SDB (AHI $\geq$ 24) increased AF odds independent of self-reported HF/CVD**
- **Obstructive Apnea- No significant association in adjusted analyses**
- **Central Apnea**
  - **CAI > 3: 3-fold higher odds of AF**
  - **Increasing CAI category associated with AF, p-trend=0.0004**
- **Cheyne Stokes Respirations-Central Sleep Apnea**
  - **4.5-fold higher AF odds in fully adjusted analyses including HF**

*p-value for linear trend<0.05

Adjusted for age, race, BMI, CVD, HTN, DM, study site, cholesterol level

Mehra R et al Arch Int Med 2009

Mr.OS Sleep

Sleep Apnea and Complex Ventricular Ectopy

SDB Quartile Odds Ratio (95% CI)	Obstructive Apnea Quartile Odds Ratio (95% CI)	Central Apnea Category Odds Ratio (95% CI)	CSR-CSA Odds Ratio (95% CI)	Hypoxia Odds Ratio (95% CI)
Reference	Reference	Reference	1.55 (1.20-2.00)	Reference
1.00 (0.79-1.27)	1.12 (0.88-1.41)	0.84 (0.69-1.02)		1.31 (1.07-1.60)
1.31 (1.04-1.66)	1.18 (0.93-1.50)	1.03 (0.79-1.35)		1.27 (0.97-1.66)
1.43 (1.12-1.82)*	1.37 (1.08-1.75)*	1.27 (0.97-1.66)		1.62 (1.23-2.14)*

SDB	Those with AHI $\geq$ 13 had 40% increased odds of CVE Increasing AHI quartile was associated with CVE p trend=0.0007
Obstructive Apnea	Those with OAHI $\geq$ 13 had 40% increased odds of CVE
Central Apnea	No significant association in adjusted analyses
CSR-CSA	Those with CSR-CSA had 55% increased odds of CVE

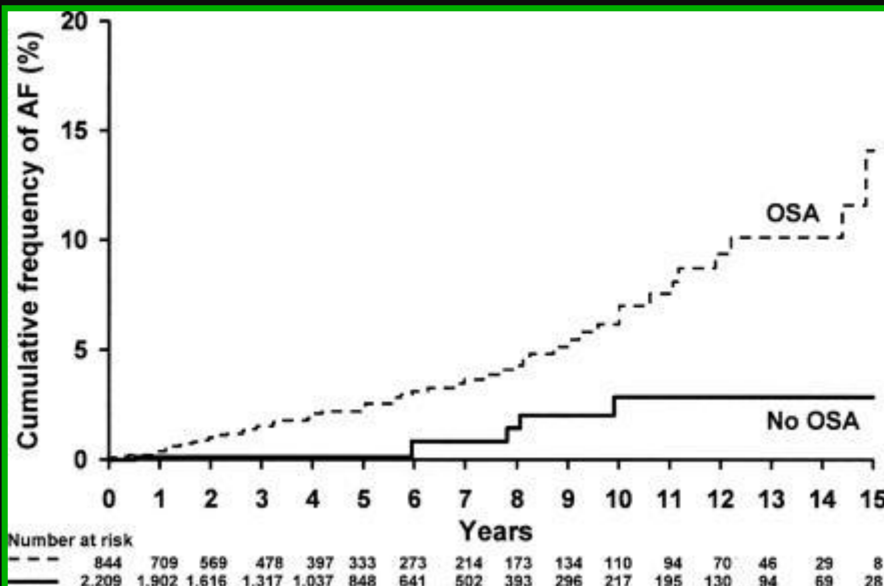
*p-value for linear trend<0.05

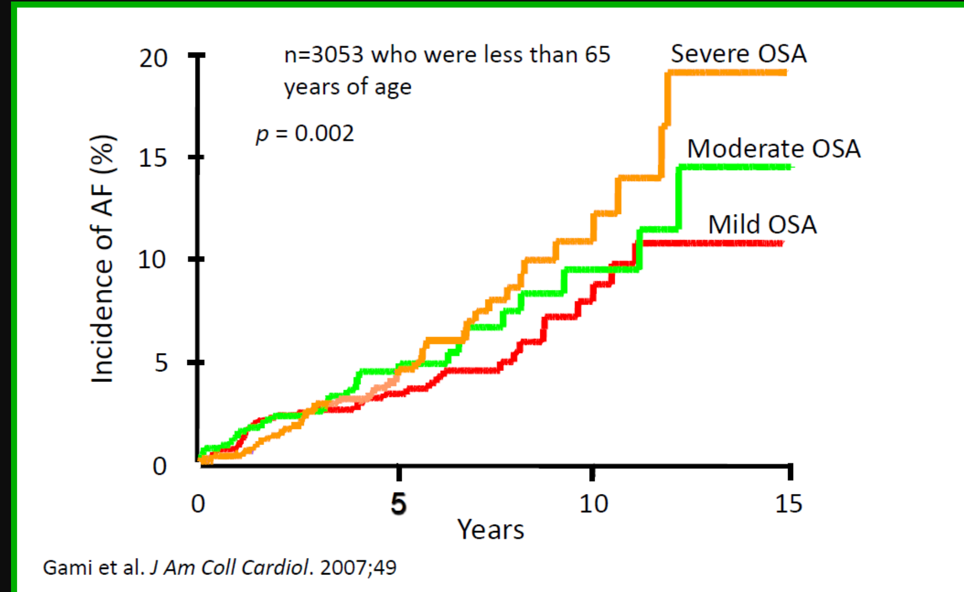
Adjusted for age, race, BMI, CVD, HTN, DM, study site, cholesterol level

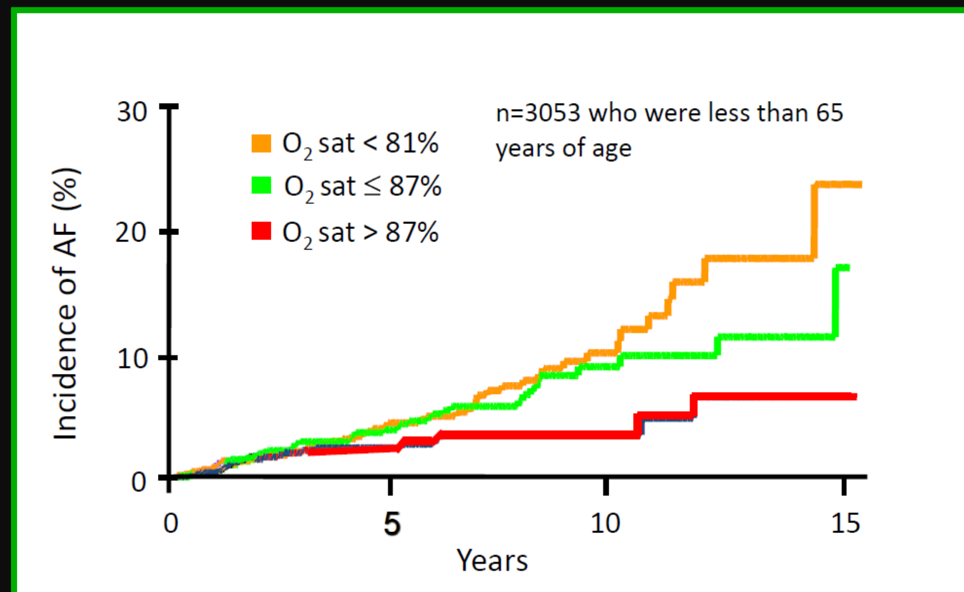
Mehra R et al Arch Int Med 2009

MrOS Sleep

Incidence of AF and Severity of OSA and Hypoxia in a Clinic-Based Cohort







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

Central Sleep Disordered Breathing Predicts Incident Atrial Fibrillation in Epidemiologic Cohorts

Anna May MD

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Obstructive and Central Sleep Apnea and the Risk of Incident Atrial Fibrillation in a Community Cohort of Men and Women

Patricia Tung, MD, MPH; Yamini S. Levitzky, MD; Rui Wang, PhD; Jia Weng, PhD; Stuart F. Quan, MD; Daniel J. Gottlieb, MD, MPH; Michael Rueschman, MA; Naresh M. Punjabi, MD, PhD; Reena Mehra, MD, MS; Suzie Bertisch, MD, MPH; Emelia J. Benjamin, MD, ScM; Susan Redline, MD, MPH

Sleep Heart Health Study

n=3329, Mean follow-up 8.2 years	Multivariable Adjusted
OAHI, per 5 increase	0.97 (0.92-1.03)
OAHI >=5	0.86 (0.64-1.16)
OAHI >=15	1.04 (0.74-1.45)
OAHI >=30	0.89 (0.53-1.50)
CAI≥5	**3.17 (1.54-6.53)**
CSA-CSR	**2.03 (1.10-3.74)**
%Total Sleep Time with SaO_2< 90%	
<1%	1.00 (reference)
1% to <3.5%	0.98 (0.65-1.48)
3.5% to <10%	1.14 (0.72-1.79)
≥ 10%	0.91 (0.56-1.48)

ORIGINAL ARTICLE

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

Anna M. May[1], Terri Blackwell[2], Peter H. Stone[3], Katie L. Stone[2], Peggy M. Cawthon[2], William H. Sauer[4], Paul D. Varosy[4], Susan Redline[3,5], and Reena Mehra[6]; for the MrOS Sleep (Outcomes of Sleep Disorders in Older Men) Study Group

[1]Division of Pulmonary, Critical Care and Sleep Medicine, University Hospitals Case Medical Center, Cleveland, Ohio; [2]California Pacific Medical Center Research Institute, San Francisco, California; [3]Brigham and Women's Hospital, Boston, Massachusetts; [4]University of Colorado at Denver, Denver, Colorado; [5]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; and [6]Sleep Center, Neurological Institute, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, Ohio

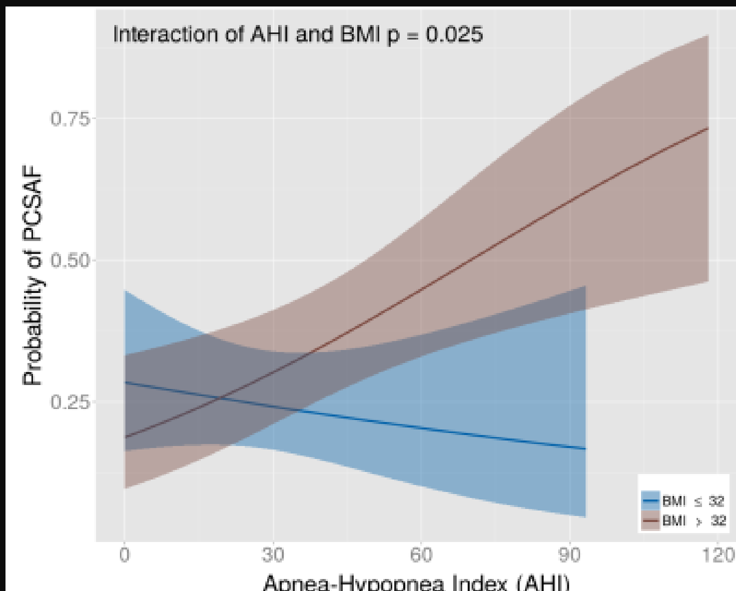
Outcomes of Sleep Disorders in Older Men Study

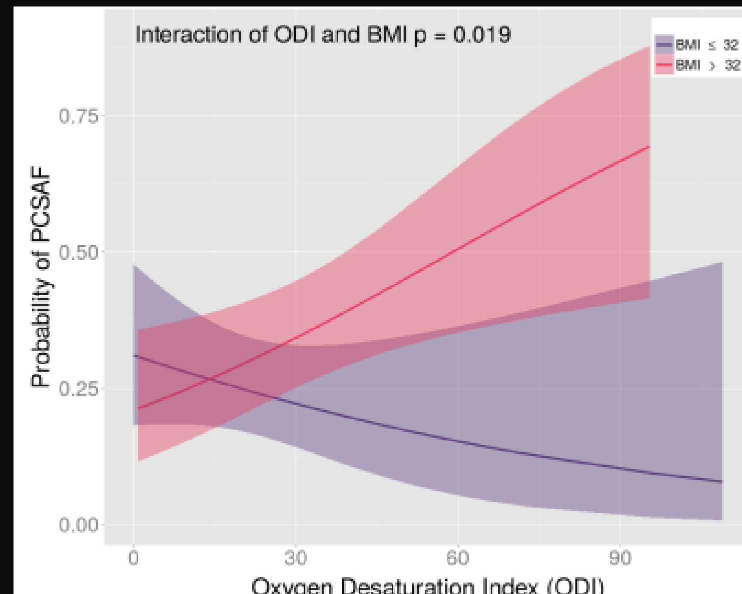
n=843, Mean follow-up 6.5±0.7 years	Multivariable Adjusted‡ OR (95% CI)
AHI, per 5 increase	1.01 (0.94 - 1.10)
AHI≥15	1.15 (0.72 - 1.84)
OAHI, per 5 increase	0.98 (0.91 - 1.07)
CAI≥5	**2.58 (1.18 - 5.66)**
CSA-CSR	**2.27 (1.13 - 4.56)**
% Total Sleep Time with SaO2<90%	
<1%	1.00 (reference)
1% to <3.5%	0.83 (0.47 - 1.47)
3.5% to <10%	1.64 (0.83 - 3.24)
≥ 10%	1.01 (0.46 - 2.24)

Tung P, et al. J Am Heart Assoc. 2017 Jul 1;6(7)
May AM, et al. Am J Respir Crit Care Med. 2015 Nov 23

Obesity as an Effect Modifier of Sleep Apnea and Post-Cardiac Surgery Atrial Fibrillation

Samer El Zarif MD





Factors	BMI ≤ 32 (N=94)		BMI > 32 (N=95)	
	OR (95%CI)	p-value	OR (95%CI)	p-value
AHI (5 unit increase)	0.94 0.83, 1.06	0.29	1.1 1.05, 1.26	*0.004*
ODI (5 unit increase)	0.90 0.77, 1.06	0.20	1.16 1.05, 1.30	*0.006*

Adjusted for age, gender, race, PAP therapy

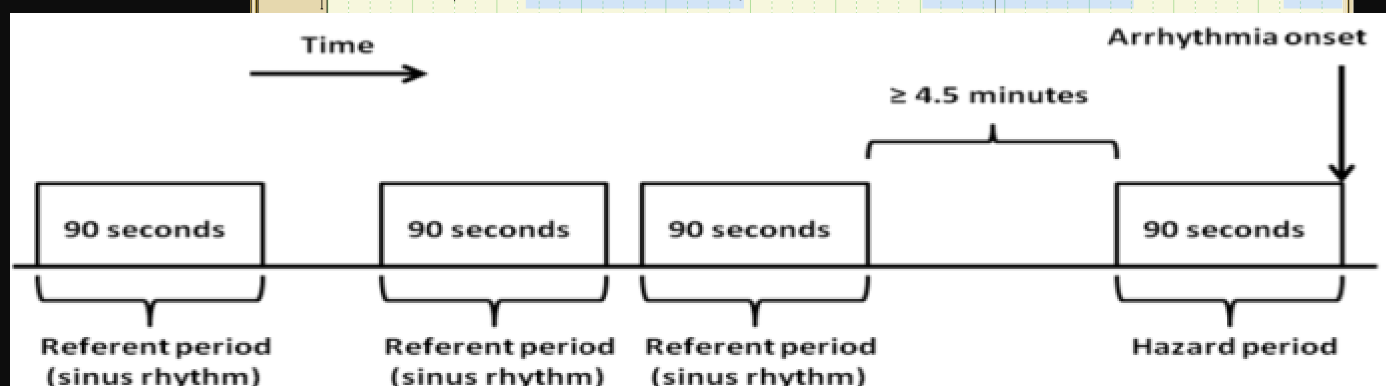
El Zarif S, et al. Associated Professional Sleep Societies, Platform Presentation 2015
Kaw R. Chest. 2017 Mar 11

Temporal Association of Arrhythmia Paroxysms and Respiratory Events

Case Crossover Study

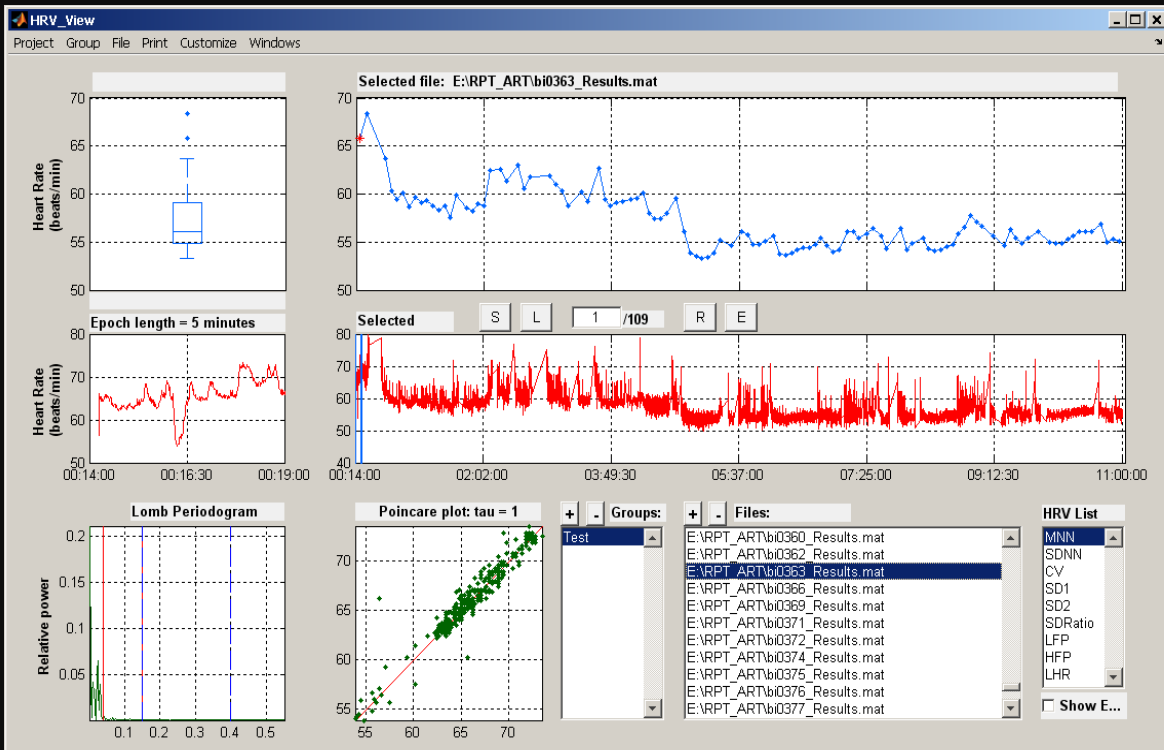
n=2816 screened for PAF and NSVT
57 participants with wide range of SDB – 62 arrhythmias (76% NSVT)

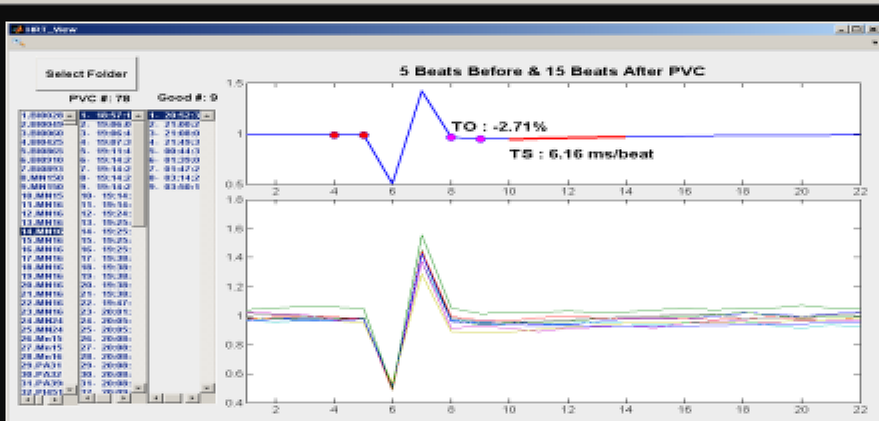
18-fold increased risk of a nocturnal arrhythmia within 90s following an apnea or hypopnea



Monahan K Journal of the American Journal of Cardiology 2009

ECG-Based Embedded Physiologic Signatures in the Polysomnogram of Incident Atrial Fibrillation





Dileep Raman MD

Primary predictors

- Low frequency (LF) band (0.04-0.15 Hz) is related to both sympathetic and parasympathetic modulation
- High frequency (HF) band (0.15-0.40 Hz) is governed by parasympathetic effects
- LF/HF power often used as a metric of sympathetic-parasympathetic balance

PSG-Based Spectral Heart Rate Variability Forecasters of Incident Atrial Fibrillation

Dileep Raman MD

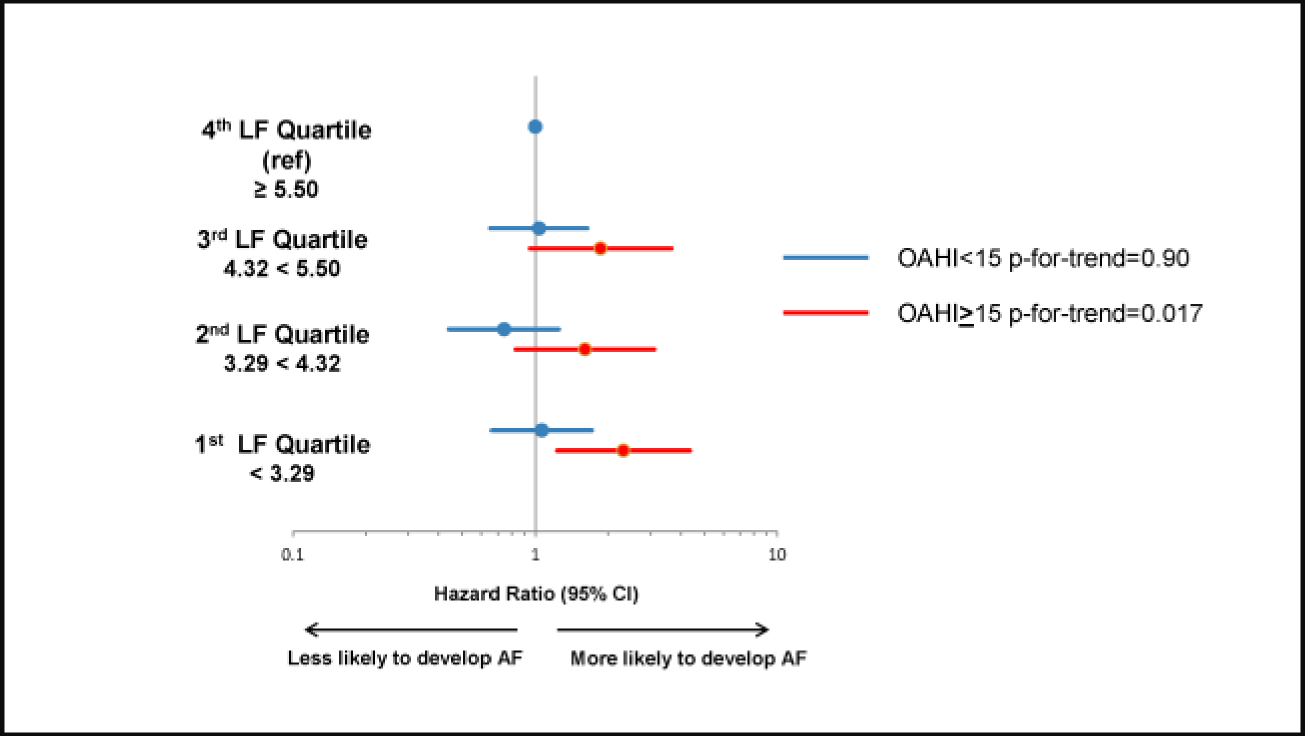
	LF	HF	LF/HF
Model 1			
Q1, n=587	**1.93 (1.37, 2.70)**	ref	**2.00 (1.44, 2.78)**
Q2, n=588	1.18 (0.81, 1.71)	0.94 (0.65, 1.36)	1.14 (0.80, 1.64)
Q3, n=588	1.24 (0.86, 1.78)	1.19 (0.84, 1.69)	0.94 (0.64, 1.37)
Q4, n=587	ref	1.67 (1.20, 2.33)	ref
p-trend	**0.0003**	**0.0008**	**<0.0001**
Model 2			
Q1, n=587	**1.46 (1.02, 2.10)**	REF	**1.46 (1.02, 2.08)**
Q2, n=588	1.01 (0.68, 1.49)	0.88 (0.60, 1.28)	0.92 (0.63, 1.34)
Q3, n=588	1.26 (0.87, 1.83)	1.14 (0.79, 1.63)	0.86 (0.58, 1.26)
Q4, n=587	REF	1.34 (0.94, 1.91)	REF
p-trend	0.09	**0.043**	**0.021**

Model 1 (unadjusted)
Model 2: Adjusted for age, race, body mass index, waist circumference, self-reported medical history including cardiovascular disease (myocardial infarction or coronary angioplasty or coronary artery bypass graft surgery or stroke), heart failure, hypertension, diabetes mellitus, anti-arrhythmic/beta blocker/calcium channel blocker medications, total cholesterol, alcohol use, COPD, and study site

Decreasing LFP/HFP ratio and LFP quartiles (reflective of reducing sympathovagal balance) was associated with increasing AF incidence.

Raman D, et al. SLEEP meeting, Platform Presentation 2015
Raman D, et al. JACC Clin Electrophysiol. 2017 May;3(5):451-460

Sleep Apnea Modifies Sympathetic HRV Measure and Incident Atrial Fibrillation



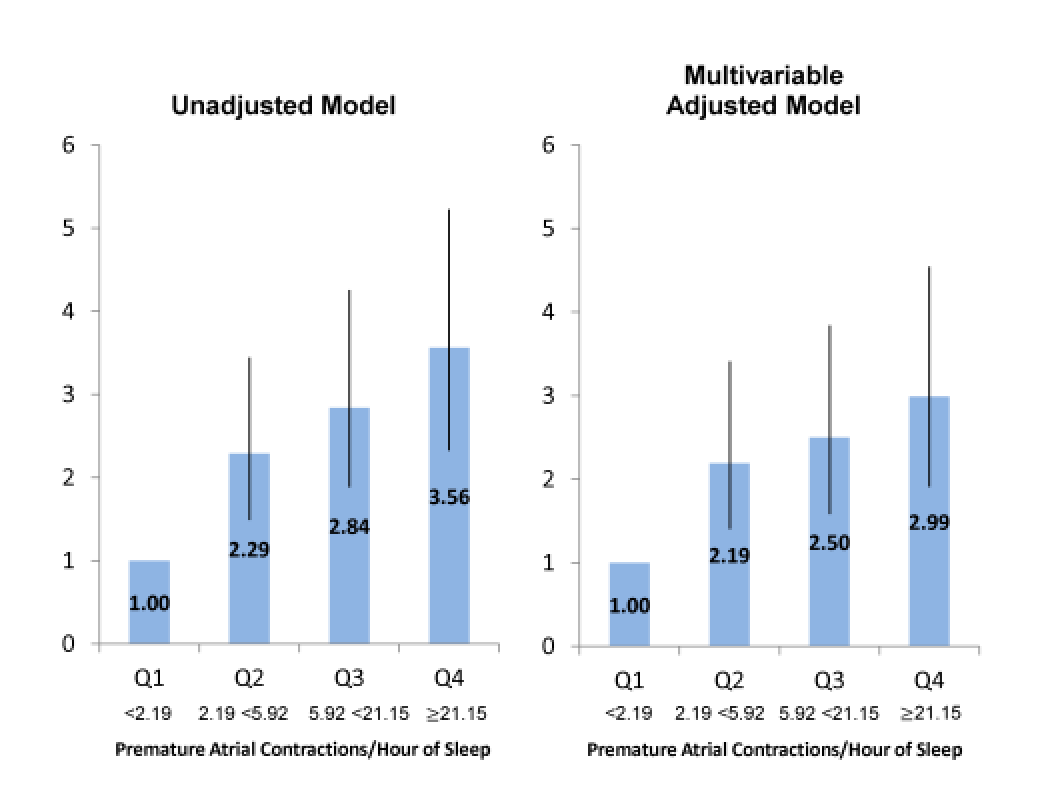
Dileep Raman MD

SDB (mainly obstructive apnea) modified the HRV-AF relationship

Suggests SDB-related enhanced sympatho-vagal influences are a risk for "cholinergic" AF development.

Raman D, et al. SLEEP meeting, Platform Presentation 2015
Raman D, et al. JACC Clin Electrophysiol. 2017 May;3(5):451-460

Atrial Ectopy on PSG ECG as a Predictor of Incident Forecasters of Incident Atrial Fibrillation



- **Strong magnitude of association of PACs and incident AF**
- **~3-fold increased risk of AF in highest quartile compared to reference: HR=2.99, 95% CI 1.94-4.62**

Model 1 (Unadjusted)
Model 2: Adjusted for age, race, body mass index, waist circumference, self-reported medical history including cardiovascular disease (myocardial infarction or coronary angioplasty or coronary artery bypass graft surgery or stroke), heart failure, hypertension, diabetes mellitus, anti-arrhythmic/beta blocker/calcium channel blocker medications, total cholesterol, alcohol use, COPD, and study site

Raman D, et al. SLEEP meeting, Platform Presentation 2015
Raman D, et al. JACC Clin Electrophysiol. 2017 May;3(5):451-460

CPAP Reduces Ectopy in a Dose-Dependent Fashion

Figure 1A. Diagnostic Portion of the Sleep Study (ectopics approximately 18/minute)

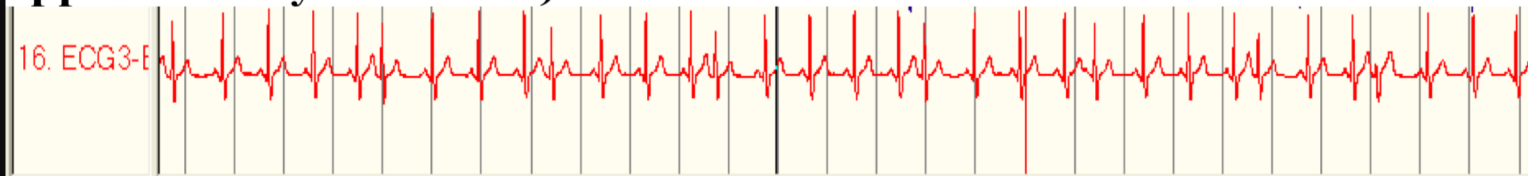


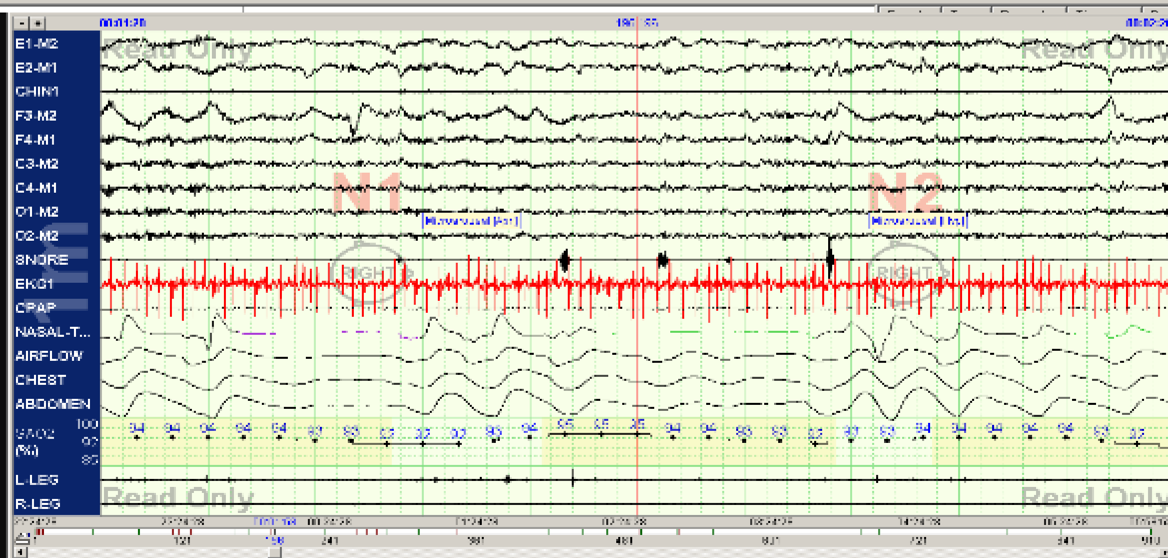
Figure 1B. Continuous Positive Airway Pressure 5 cm water pressure (ectopics,14/minute)

Figure 1C. Continuous Positive Airway Pressure 7 cm water pressure (ectopics approximately 8/minute)

Figure 1D. Continuous Positive Airway Pressure 9 cm water pressure (no ectopics)

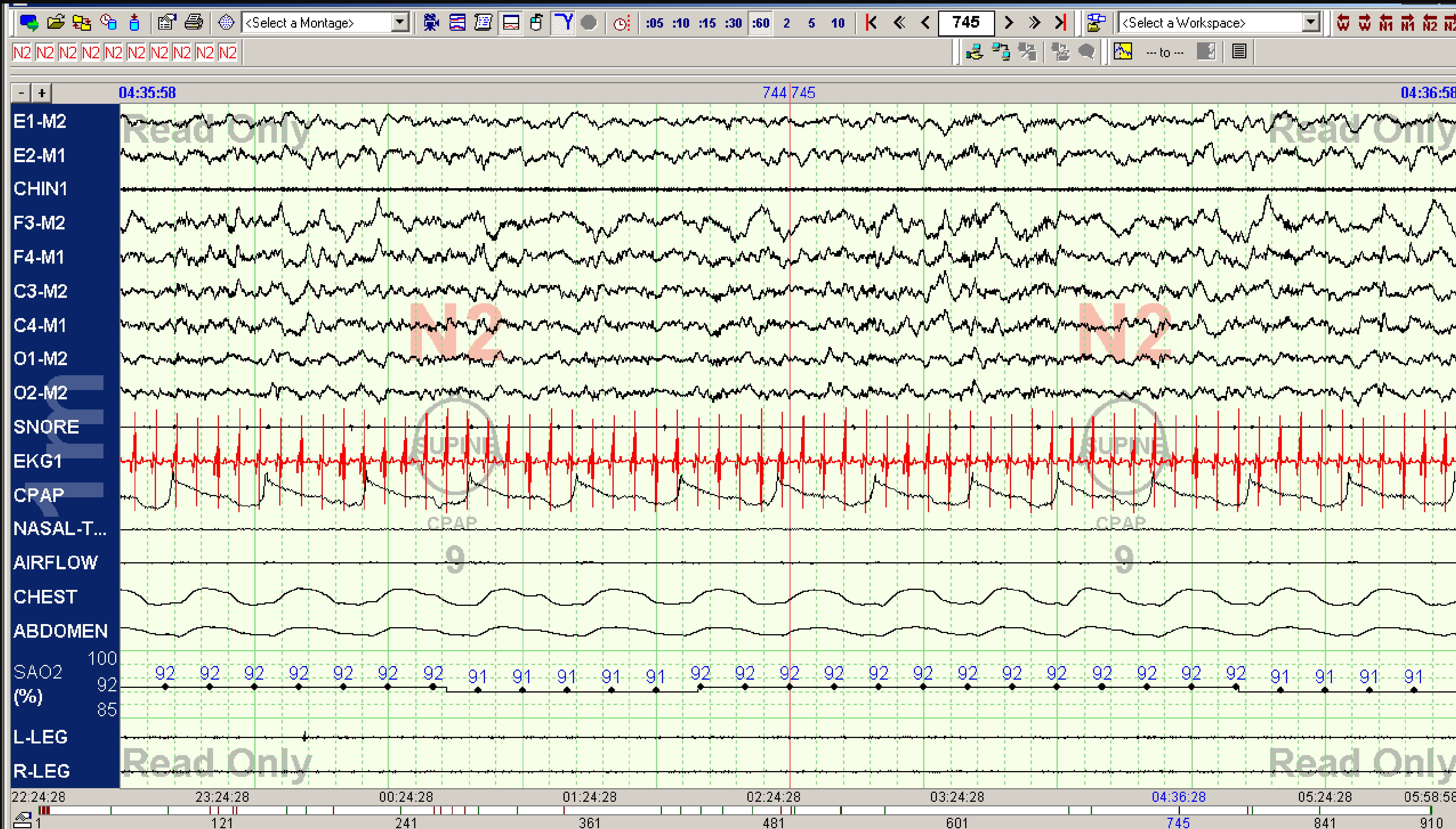
Walia H J Clin Sleep Med. 2011: 7(4)

53 yo male with atrial fibrillation and dilated cardiomyopathy
Baseline Portion of Split Night Study, HR=100-120



Walia HK. Ibrahim S, Mehra R. JCSM 2016

CPAP Titration Portion of the Study Revealing Optimal CPAP 9 cm water pressure and Conversion to Normal Sinus Rhythm (HR=70s)



Walia HK. Ibrahim S, Mehra R. JCSM 2016

Conversion of Atrial Fibrillation to Normal Sinus Rhythm on Goal CPAP Pressure

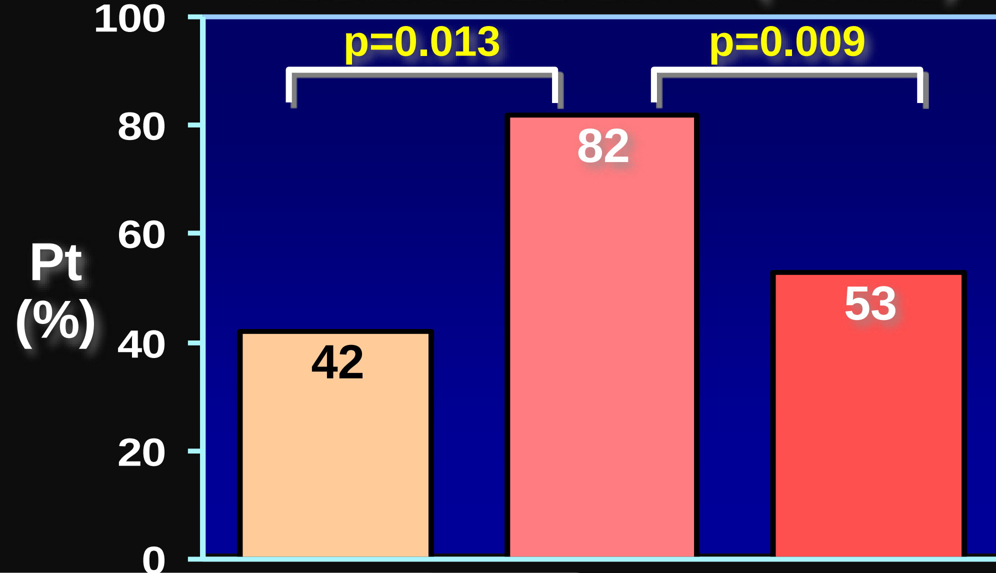
Walia HK. Ibrahim S, Mehra R. JCSM 2016

Sleep Apnea and AF Recurrence

n=118 underwent successful cardioversion

- Sleep apnea – CPAP (n=12)
- Sleep apnea – no CPAP (n=27)
- Controls – no sleep study (n=79)

Recurrence of AF (12 mo)



Untreated group:
Mean nocturnal fall in O2 sat

- Recurrence – 18%
- No recurrence – 8%

p=0.03

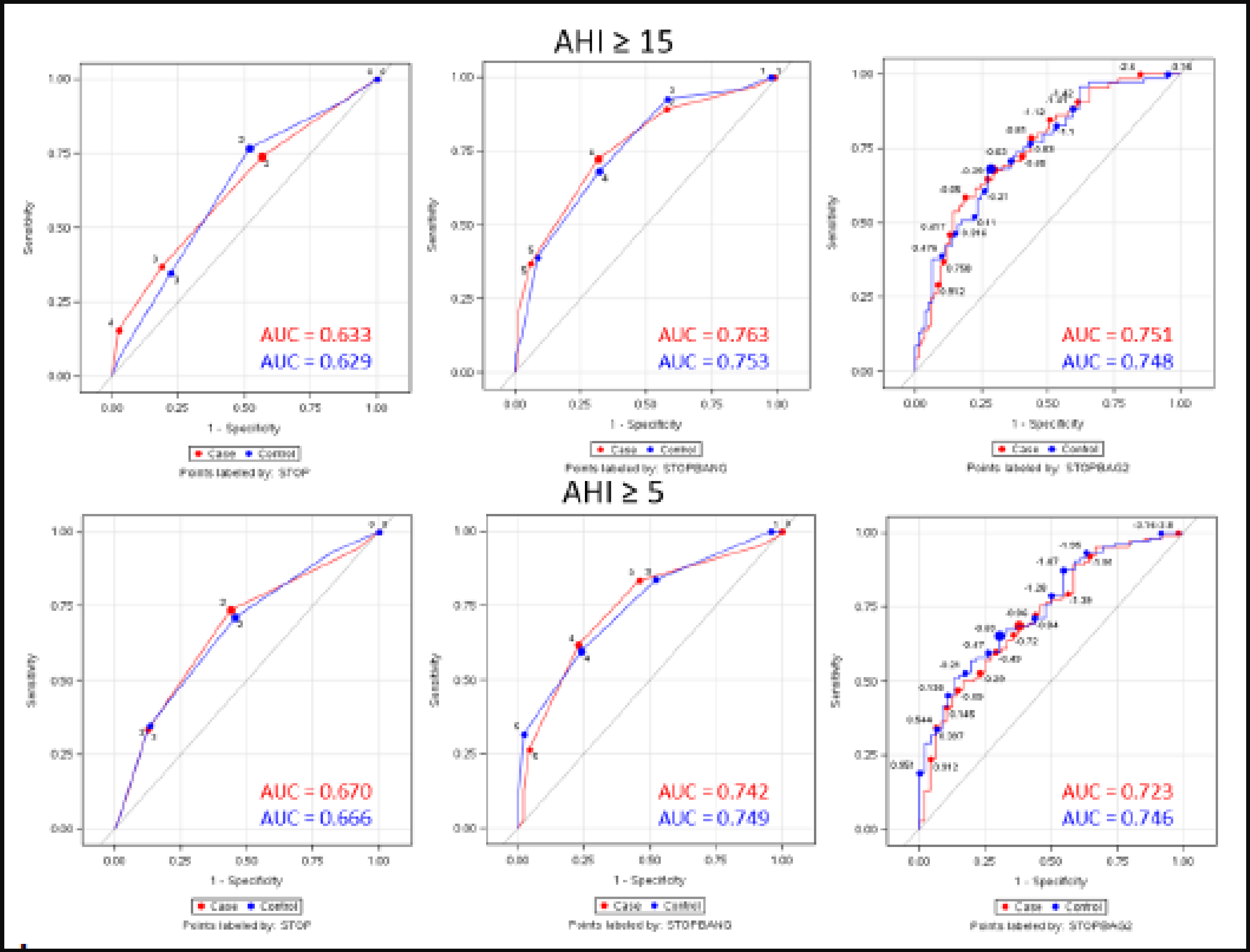
Kanagala Circulation 2003: 107: 20

Meta-analysis: n=3,995

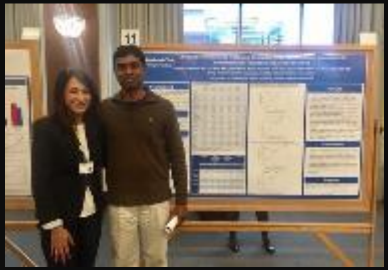
Those with OSA have a 25% greater risk of AF recurrence after catheter ablation than without OSA (RR 1.25, 95% CI 1.08-1.45)

Ng CY AJC 2011: 108

Screening for Obstructive Sleep Apnea in Atrial Fibrillation



Anna May MD



Rajesh Kandasamy MD

- NoSAS and STOP-BANG questionnaires performed most optimally in terms of sensitivity and reasonable discriminative ability of moderate to severe OSA detection in those with PAF

Kandasamy, et al. SLEEP. 2017
May AM, et al. Sleep and Breathing meeting, Madison, WI. 2017

ORIGINAL ARTICLE

Association of sleep characteristics with atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis

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n=2048

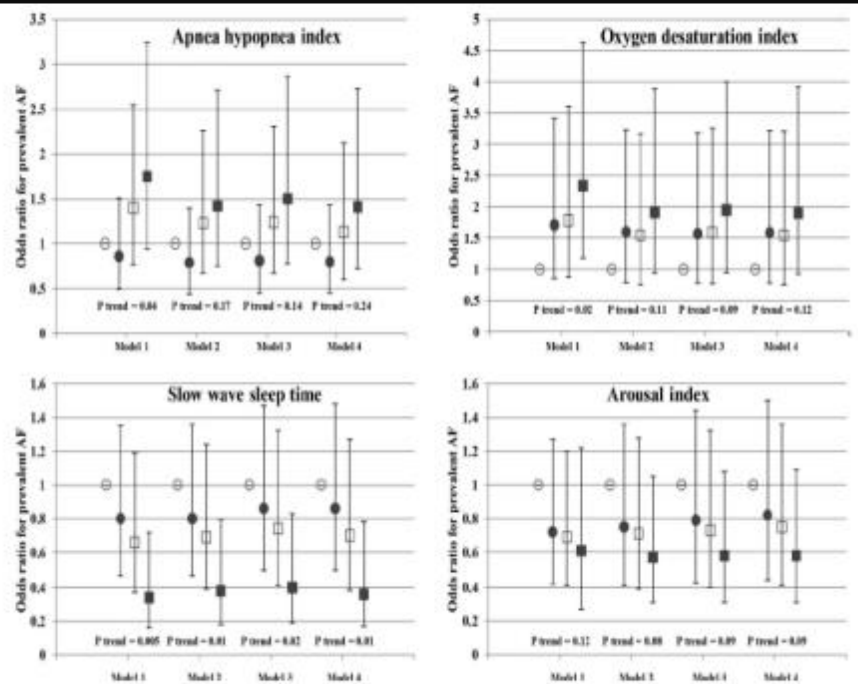
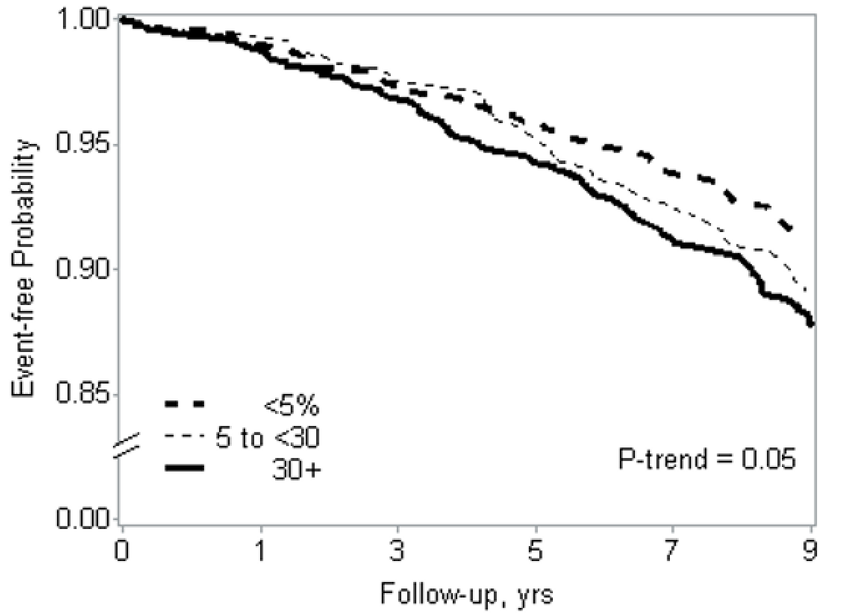


Figure 1 Adjusted OR (point estimate and 95% CI) of atrial fibrillation (AF) (per 1 SD) for: (A) common clinical cut-off points of AHI (apnoea hypopnoea index; No sleep disordered breathing: AHI <5; Mild: 5≤AHI <15; Moderate: 15≤AHI<30; Severe: AHI≥30/h) and for quartiles of (B) ODI (oxygen desaturation index), (C) SWS (slow wave sleep) time and (D) arousal index. No sleep disordered breathing group and first quartile are references. Point estimates for first through fourth quartiles are indicated by open circle (○), filled circle (●), open square (□) and filled square (■), respectively.

- **AHI and ODI was associated with AF in unadjusted but not adjusted analyses**
- **SWS inversely associated with AF**
  - **SWS cardioprotective?**
- **Arousal Index inversely associated with AF**
  - **Do arousals exert protective mechanism terminating apneic episodes?**

PLMS Associated with Atrial and Ventricular Arrhythmia



No. at risk for first incident event:

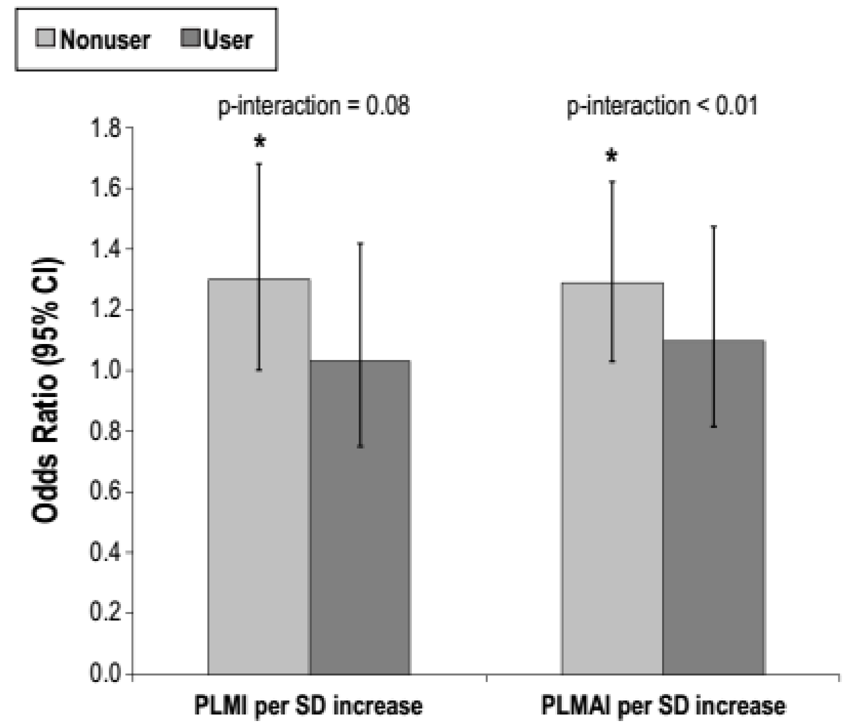
<5	289	285	259	226	187	160
5 to <30	268	263	241	219	189	153
30+	548	529	477	411	343	272

* Adjusted for clinic, age, race, body mass index, self-reported medical history (hypertension, diabetes mellitus, cardiovascular disease, stroke and heart failure), cardiovascular medication use, pacemaker placement, alcohol use, estimated glomerular filtration rate, cholesterol, and apnea-hypopnea index.

Cumulative Event-free Probability of Incident Clinically Symptomatic Atrial Fibrillation by Periodic Limb Movement Index, Age ≥76 Strata, and Multivariable Adjusted*.

May et al. Sleep Med. 2016.

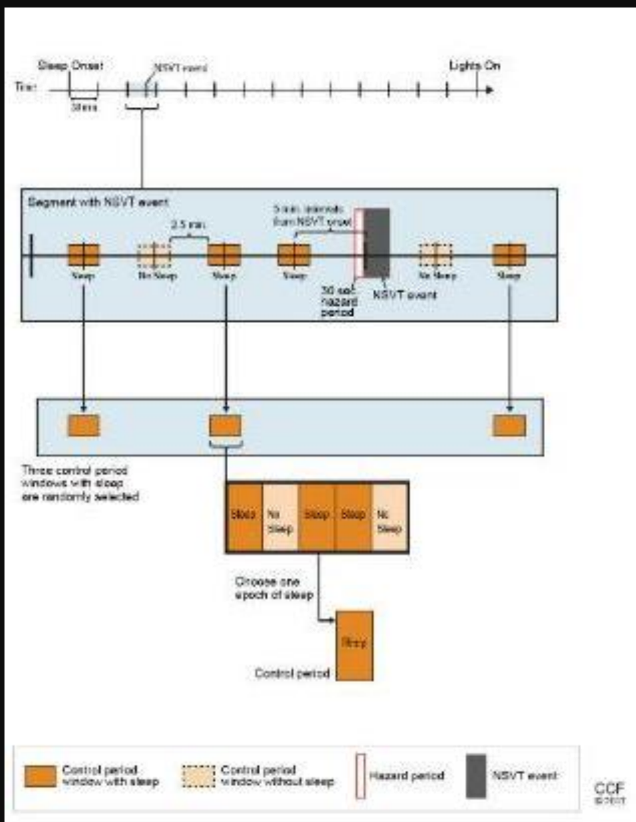
Figure 1—Non-sustained ventricular tachycardia outcome: interaction of PLMS and use of β-adrenergic or calcium channel blocking medication

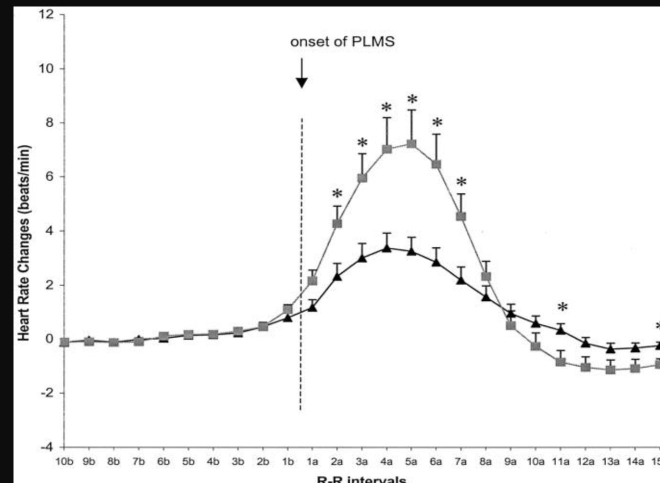


Koo et al. JCSM. 2014.

PLM-AI *(but not PLM without arousals)* Temporally Associated with NSVT Onset in Older Men

Anna May MD





	Unadjusted Odds Ratio (95% CI)	Multivariable Adjusted Odds Ratio (95% CI)
PLMS type		
No PLMS	Reference	Reference
PLMS without arousal	0.78 (0.39-1.56)	0.94 (0.46-1.93)*
PLMS with or without associated arousal	1.49 (0.70-3.17)	1.50 (0.69-3.26)*
PLMS with associated arousal	**3.31 (1.32-8.30)**	**3.50 (1.38-8.84)†**
Respiratory events	1.32 (0.76-2.30)	1.28 (0.73-2.25)‡
Minimum oxygen saturation	1.00 (0.98-1.02)	1.00 (0.98-1.01)§

* Adjusted for respiratory events, minimum saturation, and arousals
† Adjusted for respiratory events, minimum saturation, and non-PLMS-associated arousals
‡ Adjusted for minimum saturation, arousals, and any PLMS
§ Adjusted for respiratory events, arousals, and any PLMS
CI = confidence interval, PLMS = periodic limb movement during sleep

May AM et al. SLEEP. 2017, Platform presentation

Current State of Knowledge

- Unexplained AF risk is partially attributable to SDB
- Accruing data implicate autonomic dysfunction and cardiac structural alterations as culprits
- SDB-AF epidemiologic data
  - High strength of association OR~4 after consideration of confounders
  - Dose response relationships
  - Temporal relationship between apneas/hypopneas and AF paroxysms
  - Central versus obstructive sleep apnea may pose more of a risk of AF development
- Retrospective data suggest that sleep apnea treatment reduces recurrence of AF
- SDB associated with sudden nocturnal cardiac death
- SWS and arousal index are possibly cardio-protective
- Possible role of PLMS with arousal in cardiac arrhythmia development

Important Knowledge Gaps to be Addressed

- Mechanisms Mediating SDB and AF
  - Structural, Inflammation, Oxidative Stress, Neurohumoral, Vascular Interactions
  - SDB effects independent of underlying cardiac structure
  - Obesity-Sleep Apnea interactions
- Best Markers of Risk
  - Do nocturnal EP markers predict incident AF?
- Subgroup Susceptibilities
  - Age, race, sex, underlying cardiac disease, genetic susceptibilities
- SDB Physiologic Triggers
  - Hypoxemia versus hypercapnia, ANS
  - OSA thresholds for treatment in AF
- SDB Predictiveness of Arrhythmia Development
- Treatment implications
- OSA prediction in AF


Thirajet Leelapakpien, MD


Jenie George, MD


Joseph Michaels, MD

Progress toward the prevention and treatment of atrial fibrillation: A summary of the Heart Rhythm Society Research Forum on the Treatment and Prevention of Atrial Fibrillation, Washington, DC, December 9–10, 2013

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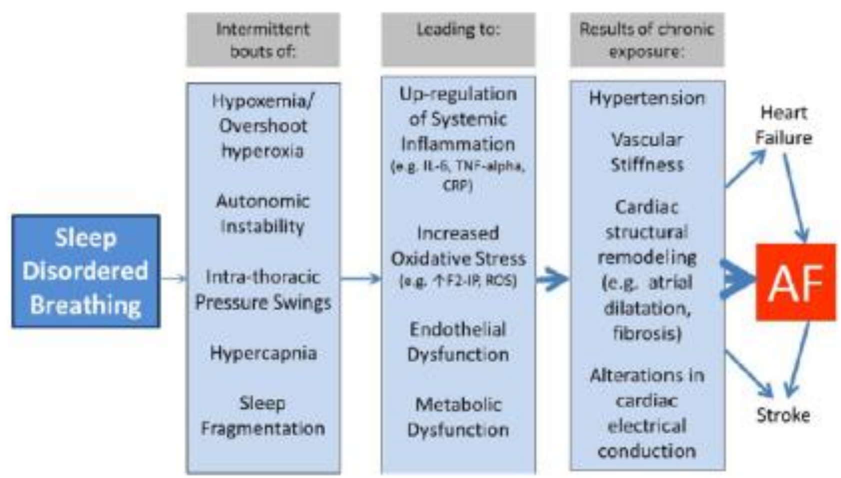


Figure 3 Mechanisms linking sleep disordered breathing (SDB) with risk of AF. Continuous positive airway pressure (CPAP) can help to reduce the burden of SDB and thus may be a useful tool in the prevention of AF, as well as the intermediate pathologic processes.

Sleep and Cardiopulmonary Disease

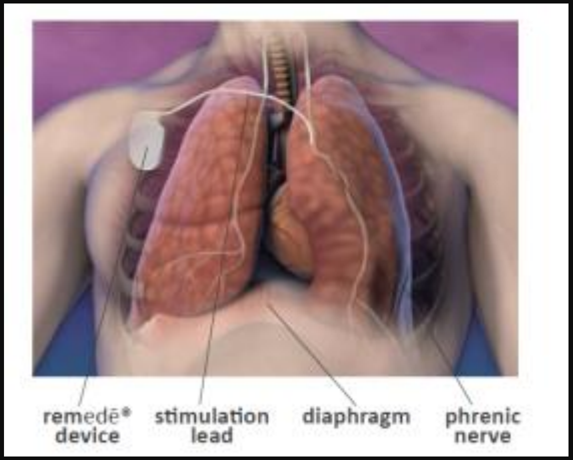
NHLBI-funded Sleep Related Respiratory and Electrophysiological Atrial Fibrillation Predictors

Predictors of AF in a longitudinal study of ~3000 participants of the MrOS Sleep Study

NHLBI-funded RCT to examine effect of sleep apnea treatment on CV biomarkers

SASS
Sleep Apnea Stress Study

Transvenous Phrenic Nerve Stimulation Device for CSA Treatment



NHLBI-funded
Sleep apnea and
Atrial Fibrillation Electrophysiology:
Biomarkers and Evaluating Atrial
Triggers

SAFEBEAT

PVDOMICS

NHLBI-funded multicenter cohort study to phenotype PHTN including sleep testing

NHLBI ARRA funded trial
Multi-center trial to examine utility of nocturnal supplemental oxygen in treating patients at high CV risk with sleep apnea

HeartBEAT
Heart Biomarker Evaluation In Apnea Treatment

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- John Barnard PhD
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- American College of Chest Physicians T Franklin Williams
- Lerner Research Institute Center of Excellence Honorable Mention Award

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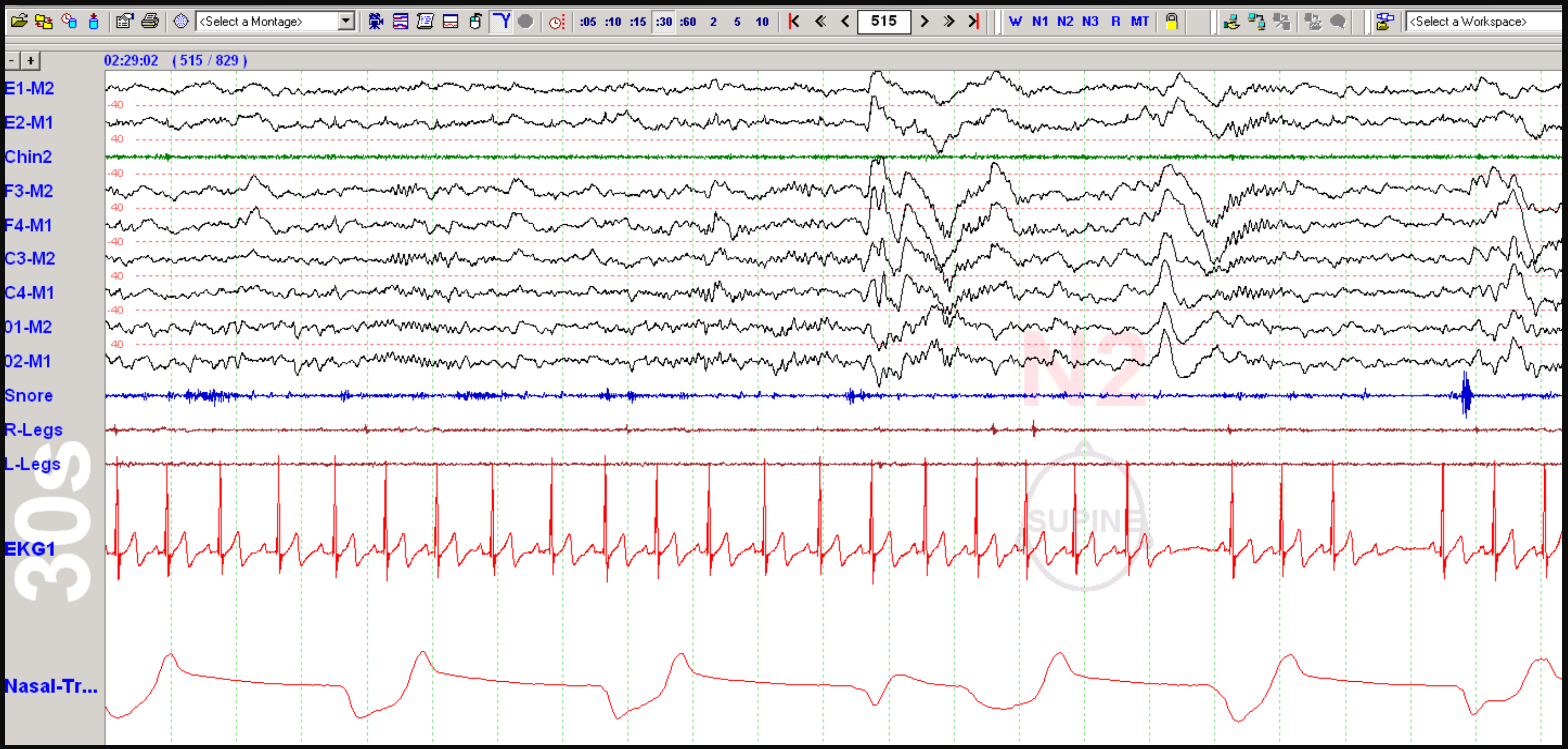
EKG2
EKG1
30S
R



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F3-M2
F4-M1
C3-M2
C4-M1
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EKG1
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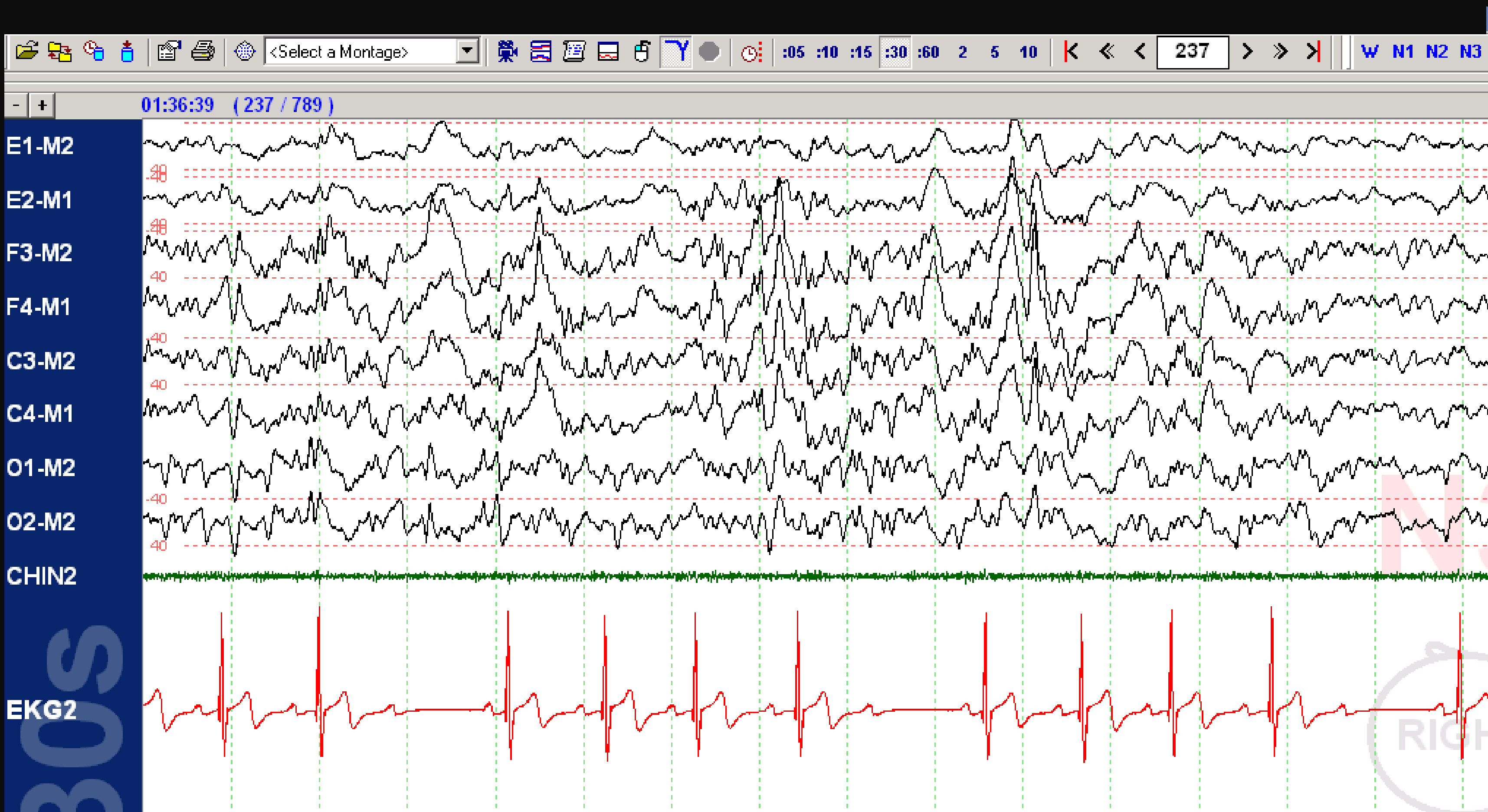
30S
N2
SUPINE



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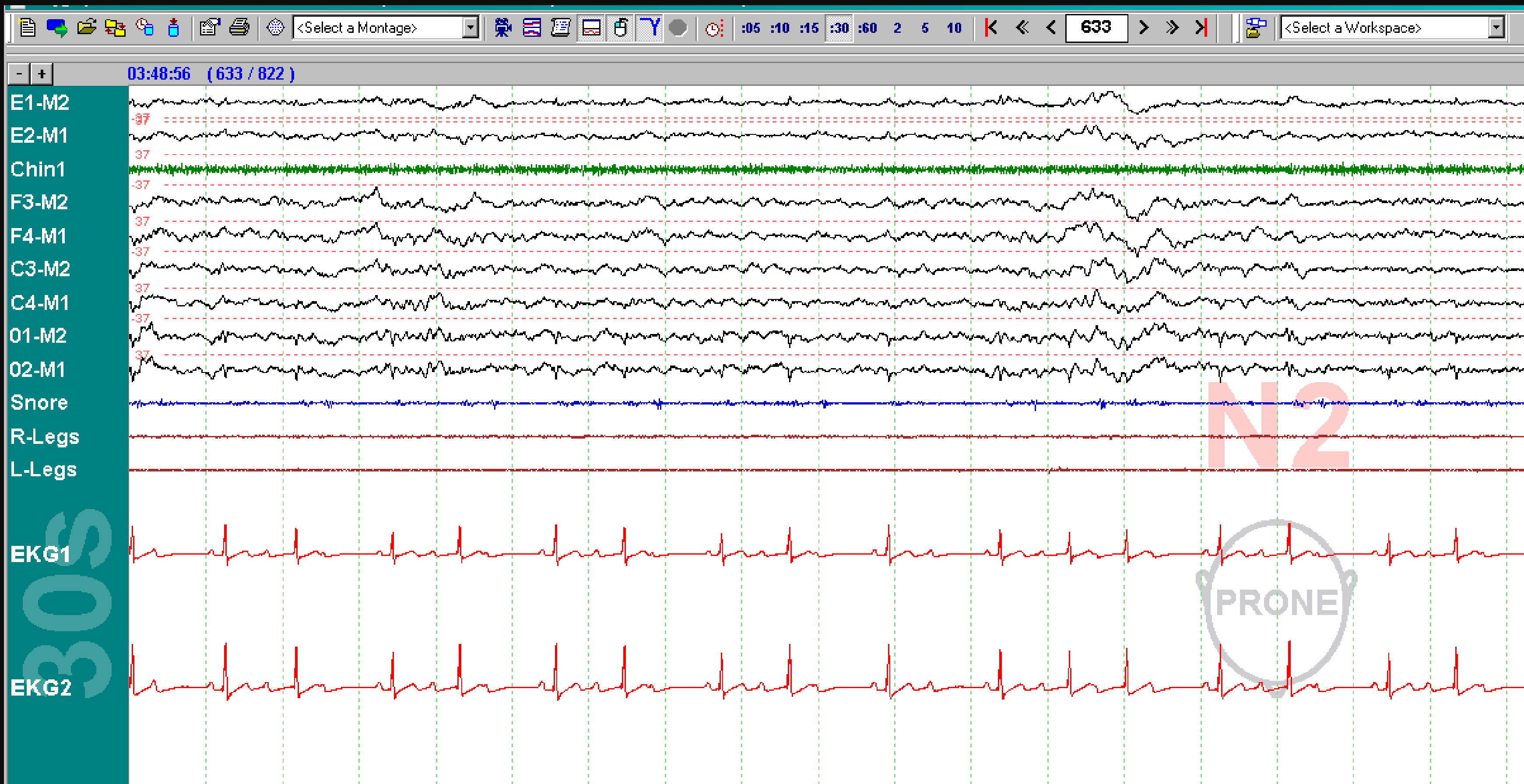
O1-M2
O2-M2
CHIN2
EKG2
30s



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F4-M1
C3-M2
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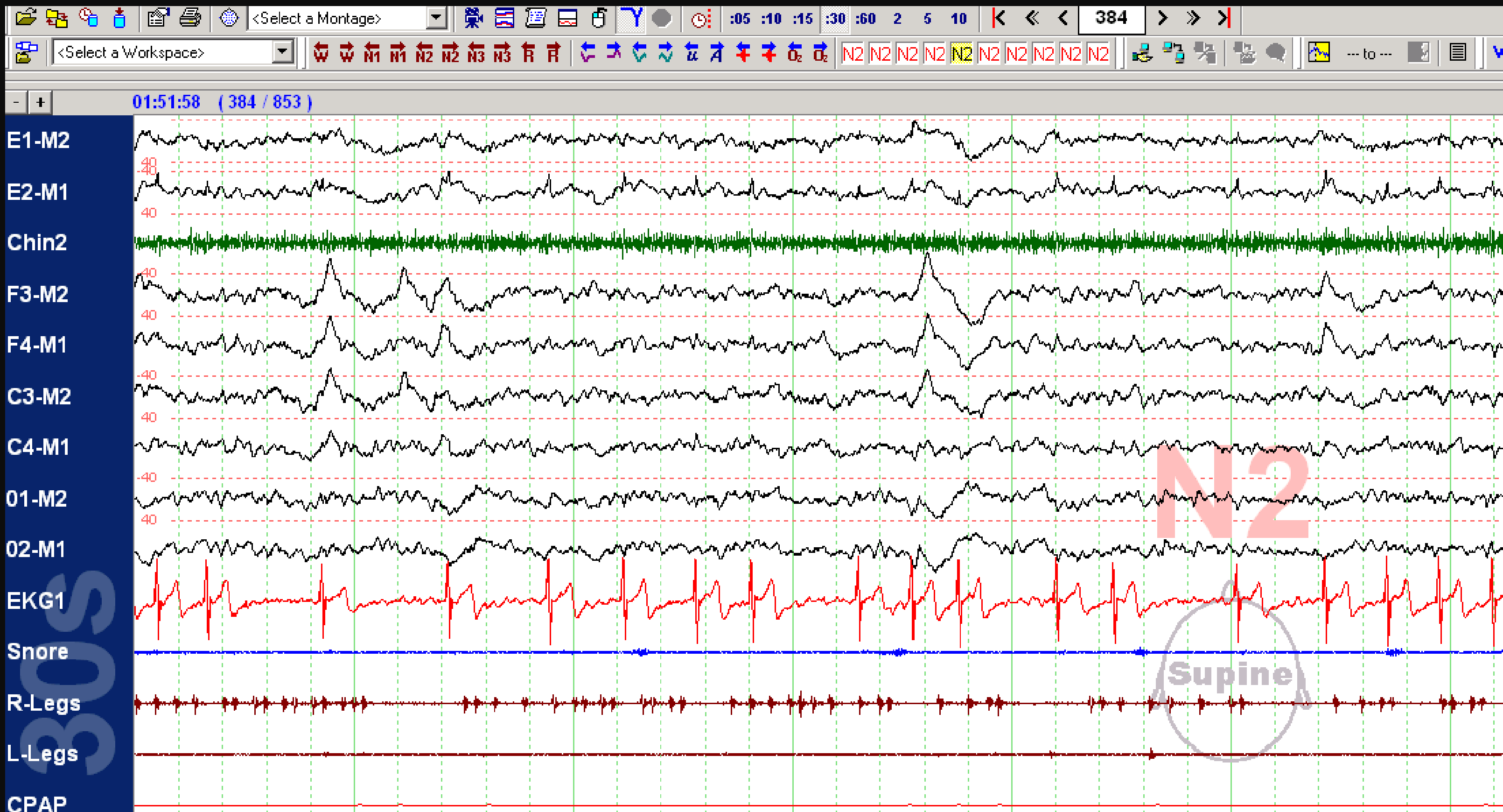
Snore
R-Legs
L-Legs
EKG1
EKG2
30S
N2
PRONE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F3-M2
F4-M1
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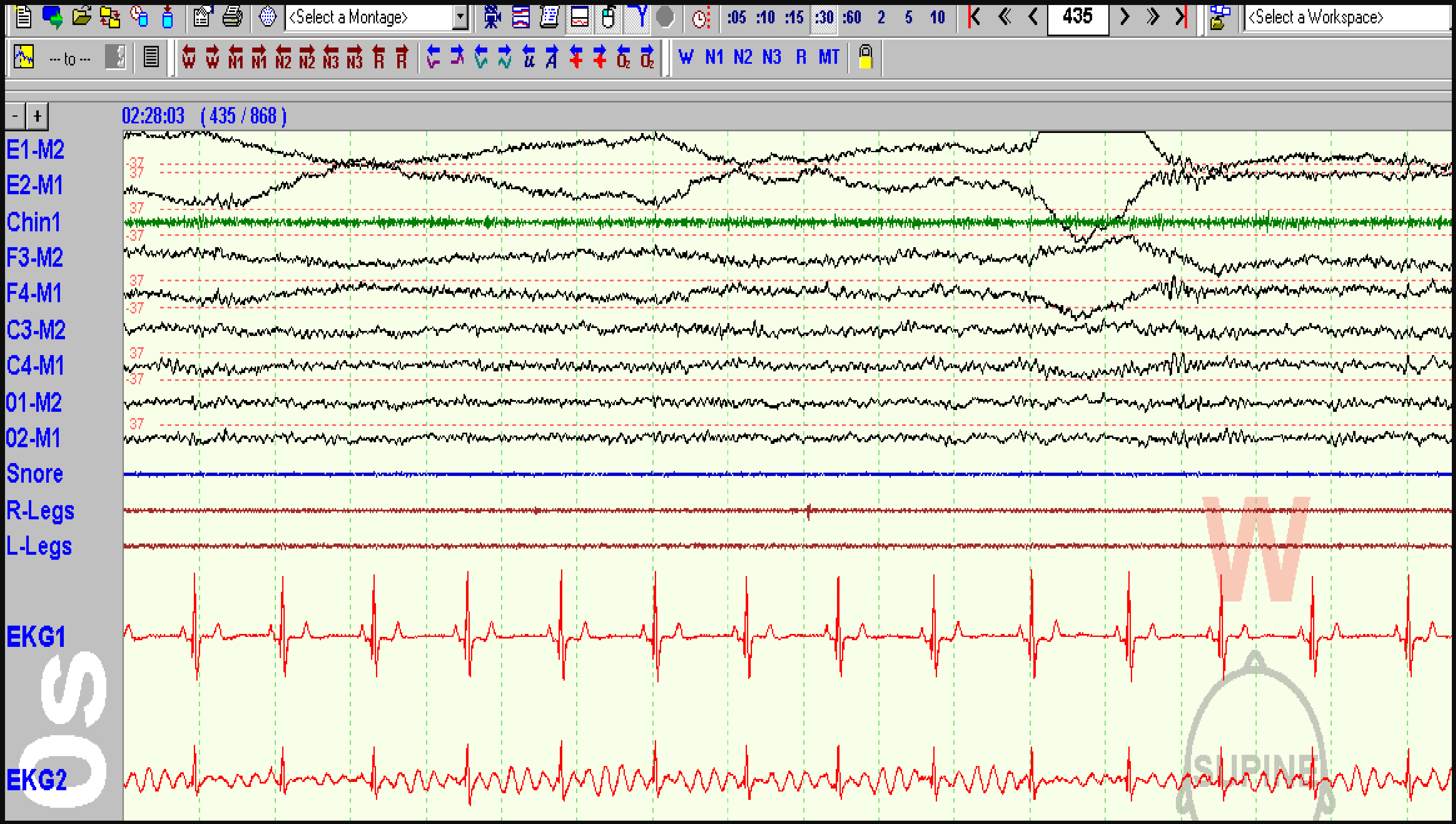
02-M1
EKG1
Snore
R-Legs
L-Legs
CPAP
30S
N2
Supine



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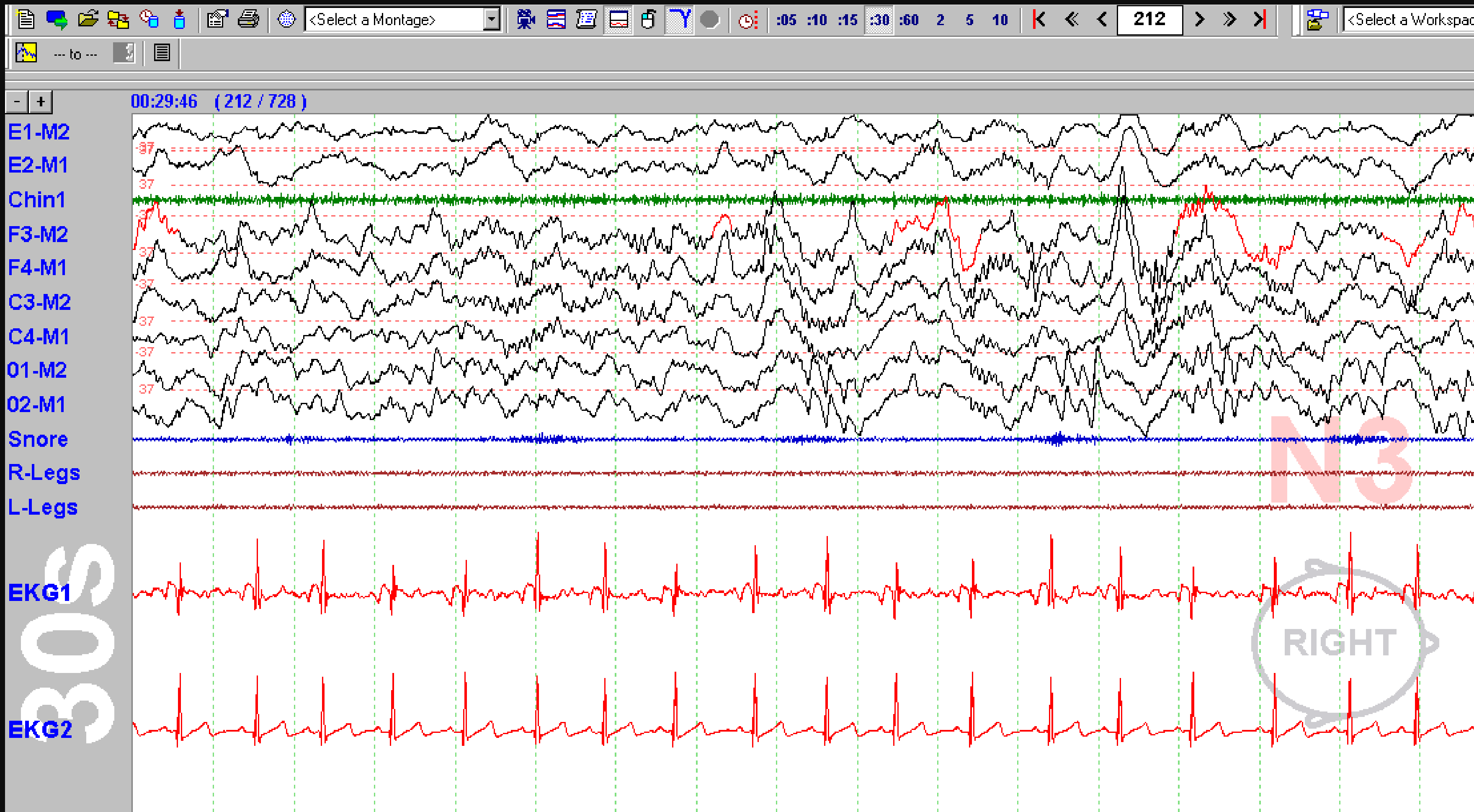
L-Legs
EKG1
EKG2
W
SUPINE



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F4-M1
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C4-M1
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02-M1
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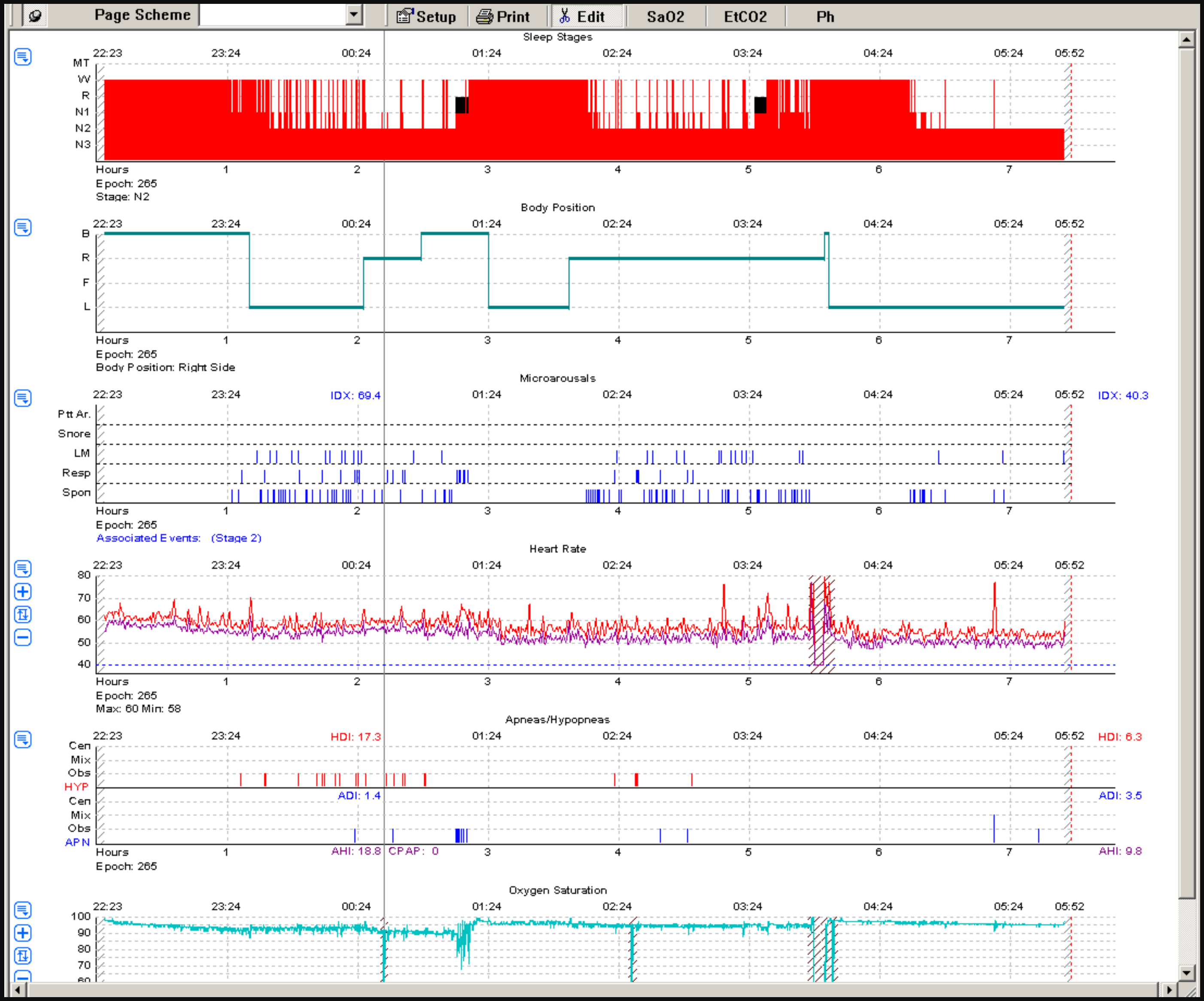
EKG2
30S
N3
RIGHT



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Body Position
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