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Polysomnographic Heart Rate Variability Indices and Atrial Ectopy Associated with Incident Atrial Fibrillation Risk in Older Community-dwelling Men

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Abstract

Background—Autonomic dysfunction contributes to atrial fibrillation (AF).

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Objective—We hypothesized that polysomnogram (PSG)-based heart rate variability (HRV) autonomic function biomarkers are associated with incident AF and these associations are modified by measures of sleep disordered breathing (SDB).

Methods—2350 participants of a multi-center prospective study (Outcomes of Sleep Disorders in Older Men Study) without baseline AF underwent sleep studies with incident adjudicated AF follow up (8.0 ± 2.6 years). Cox proportional hazard models were used to analyze sleep study-ECG spectral HRV indices [low and high frequency power (LF, HF), LF/HF] and time domain indices [mean of normal to normal beats (MNN), short and long term variability (STV, LTV) and STV/LTV] and premature atrial contractions (PACs) and incident AF (HR and 95% CI). Statistical interactions between HRV and SDB were examined. Models were adjusted for age, race, body mass index, waist circumference, cardiac medications, co-morbid diseases, alcohol use and study site.

Results—Lower LF/HF and lower LF were associated with higher AF incidence (LF/HF Q1 vs. Q4: 1.46, 1.02–2.08, LF Q1 vs. Q4: 1.46, 1.02–2.10). Higher STV/LTV was associated with an increased risk of AF (p-trend= 0.028). The highest PAC quartile had a 3-fold increased AF risk (2.99, 1.94–4.62) compared to the lowest quartile. A significant interaction of obstructive apnea was observed in the LF-AF relationship (0.045).

Conclusions—Sleep-related reduced sympathovagal balance (LF/HF) and increased atrial ectopy are independently associated with future AF; a relationship modified by obstructive apnea.

Keywords

atrial fibrillation; heart rate variability; sleep apnea

Introduction

Sleep disordered breathing (SDB), a highly prevalent disorder, is characterized by repetitive upper airway collapse and attendant intermittent hypoxia, intrathoracic pressure alterations and autonomic nervous system fluctuations. SDB prevalence is increasing and is 2–4 fold more common in men [1] and upwards of 20% in elderly men. [2] SDB-related autonomic dysfunction likely contributes to atrial fibrillation (AF) development, [3] the latter associated with considerable morbidity and mortality. Similar to SDB, AF prevalence is expected to rise given the increased percentage of the aged population. [4]

Enhanced vagal activity during apnea and hypopnea events are punctuated by sympathetic nervous system activation, thereby creating conditions for electrical remodeling and cardiac arrhythmogenesis. Muscle sympathetic nervous system activation is augmented in sleep apnea, findings that persist during wakefulness, and improve with treatment. [5] In a canine model, right ganglionated plexus ablation inhibited apnea-induced AF. [3] Thus, SDB may represent a novel target for AF prevention and treatment strategies as underscored in a recent report. [6]

Furthermore, there are 1.1 million polysomnograms (PSGs) performed annually in the United States alone, mainly to test for SDB. [7] Given the high SDB prevalence and under-diagnosis, efforts are underway to increase recognition and enhance efficiency via the use of

home sleep apnea testing (HSAT) resulting in further increases in sleep testing volumes. Sleep testing, a potential untapped resource, may provide physiologic signatures to predict adverse health outcomes such as AF. Although there is a high throughput of sleep studies which include standard respiratory channels in PSG and HSAT, there are no consistent recommendations to include the ECG signal. [8]

We investigate whether PSG-based cardiac electrophysiologic indices, heart rate variability (HRV) and atrial ectopy, the latter recognized to predict AF [9], are associated with increased risk of AF development. We focus on ECG measures most likely to represent biologic correlates/precursors of AF development, i.e. HRV as a marker of autonomic function and PAC burden as an indication of pulmonary vein trigger potential. We leverage a large community-based cohort with careful collection of objective sleep measures in a group of older men at increased for AF and its attendant morbidity. Given autonomic fluctuations which accompany apneas and hypopneas, we also examined the effect modification of SDB indices.

Methods

PARTICIPANTS AND STUDY DESIGN

The Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep Study) is a prospective, observational ancillary study of the Osteoporotic Fractures in Men Study (MrOS study). In the parent MrOS study, 5,994 community-dwelling men aged 65 and older able to ambulate without assistance, and without history of bilateral hip replacement were initially enrolled in 2000–2 at six centers (Birmingham, Alabama; Minneapolis, Minnesota; Monongahela Valley near Pittsburgh, Pennsylvania; Palo Alto, California; Portland, Oregon; San Diego, California) underwent enrollment. The MrOS study design, methods, and demographics were previously published.[10–12]

Of the 3135 MrOS Sleep Study participants who completed a repeat visit from December 2003 through March 2005, 179 did not participate in polysomnography (PSG) due to refusal or treatment of SDB and 45 men had a failed sleep study (1.5%). Of the 2911 participants with a valid sleep study, 121 had pacemakers or poor ECG quality, 136 had prevalent AF identified on the baseline polysomnogram, 266 did not have 5 continuous minutes of ECG data without artifact or ectopy and 38 men were without data on adjudicated AF events. Thus, the final analytic sample included 2350 participants with a mean duration of follow up 8.0 ± 2.6 years. (Figure 1). Each site and the study coordinating center received ethics approval from their institutional review board. Written informed consent was obtained from all participants.

DATA COLLECTION

Electrophysiologic Data Analysis—Heart Rate Variability (HRV) signal processing analyses were performed from the lead I ECG signal (sampled at 250 Hertz) of the polysomnogram. Pre-processing of the ECG channel was conducted via sequential automated and subsequent manual scoring involving visual inspection of the PSG ECG data using the Somte software (Compumedics ®). Automated analyses were applied to the ECG

data with subsequent manually review (high inter- and intra-observer reliability (0.98–0.99) for ventricular and atrial ectopic beats [13]) to identify normal sinus beats, ventricular ectopic beats (premature beat with QRS duration >120 milliseconds), atrial ectopic beats (premature beat with QRS duration <120 milliseconds) and artifact. Prior work supports a Premature atrial contractions were identified per hour of sleep.

To compute HRV analyses, as per standard recommendations [14], all 5 minute segments (standard duration to ensure stationarity of the ECG time-series) from the PSG ECG recordings of continuous non-overlapping ECG, i.e. without ectopy or artifact as informed by pre-processed ECG data were identified-- only normal sinus beats were used for analyses [15]. Artifact rejection algorithms intrinsic to the HRV analysis were also used to exclude those segments with heart rate lower than 30 beats per minute or greater than 180 beats per minute or instantaneous heart rate change exceeding 80 beats per minute between two consecutive R-R intervals.

Time series measures analyzing normal-normal (NN) R-R intervals included conventional time domain HRV measures such as MNN (mean of the NN intervals) and those derived from the Poincare' plot. Here NN refers to intervals between normal heartbeats resulting from sinus node depolarizations that are detected between adjacent QRS complexes of continuous artifact free ECG. Specific parameters from the Poincare' analysis include short- and long- term variability measures (STV and LTV, respectively). In the analysis, consecutive beat-to-beat data is analyzed as a scatter gram and the distribution of points along orthogonal directions that define the minor and major axes of a hypothetical ellipse that fits the data represent the STV and LTV.

Frequency-based or spectral HRV measures were also considered as primary predictors and analyzed using approaches for the analysis of non-uniformly based R-R interval data for spectral analyses of the R-R time series [16]. Using this approach, the normalized low frequency power (LF, from 0.04–0.15Hz) and the normalized high frequency power (HF, from 0.15–0.4Hz) were calculated. The activity in the HF frequency band is considered to be primarily due to parasympathetic activity of the sinoatrial node and the LF region is generally considered to reflect sympathetically mediated activity [17]. The LF to HF ratio (LF/HF) is often used as a measure of sympathovagal balance.

Adjudicated Atrial Fibrillation and Follow-Up—Participants were queried every four months about cardiovascular events requiring hospitalization or emergency room visit by mailed questionnaire and/or telephone contact (>99% response rate). AF events were then centrally adjudicated by a board-certified cardiologist using a pre-specified standard protocol utilizing medical records and supporting documentation. AF events were defined using similar criteria used in prior studies [18–20] as those resulting in symptoms or an emergency department visit, hospitalization and/or prolongation of a hospitalization or a procedure directly attributable to AF.

Symptoms considered for adjudication included fatigue, palpitations, lightheadedness, pre-syncope, syncope, chest pain, or dyspnea. Documentation required for an adjudicated AF event included one or more of the following: emergency medical services notes and/or

rhythm strips, electrocardiography (including stress testing), in-hospital telemetry, ambulatory electrocardiography (Holter monitor and/or event monitor), pacemaker or defibrillator telemetry (for those patients with a device already implanted), or invasive cardiac electrophysiology testing. Atrial fibrillation and atrial flutter events included either of these tachycardias as well as any cardioversion procedures to restore normal sinus rhythm. As part of the tri-annual postcard contact, participants were asked about SDB treatment. Among those without AF, 575 died and 63 terminated during the follow-up period and were right censored.

Polysomnography Data—An unattended 14-channel home polysomnogram (Safiro, Compumedics, Inc.®, Melbourne, Australia) was performed within 6.9 ± 15.8 days from the MrOS Sleep visit and was set up by certified staff in the participant's home for one night. The sleep study involved use of C_3/A_2 and C_4/A_1 electroencephalograms, bilateral electrooculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow (by nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry, lead I EKG (250Hz), body position, and bilateral leg movements. Apnea was defined as complete or near complete cessation of airflow for more than 10 seconds. The event was categorized as obstructive if effort persisted on thoraco-abdominal inductance channels or as central if there was no effort detected. Hypopneas were scored if clear reductions in breathing amplitude (at least 30% below baseline breathing) occurred, and lasted greater than 10 seconds with a drop in arterial saturation of 3% or more.[21] The inter-scorer reliability for the apnea hypopnea index (AHI) was high (ICC=0.99).[22] SDB severity was defined by the apnea hypopnea index (AHI, total number of apneas and hypopneas). The obstructive apnea hypopnea index (OAHI) was calculated as the number of obstructive apneas and hypopneas associated with a =3% desaturation per hour of sleep and central Apnea Index (CAI) was calculated as the number of central apneas per hour of sleep.

Covariates—Questionnaires were completed by all participants at the sleep visit. Demographic information, personal habit, and medical history data were collected. Participants were asked to provide all current medications used within the last 30 days.[23]; prescription and nonprescription medication information was collected, entered into an electronic database and matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).[23] Cardiovascular medications included calcium channel blockers, non-ophthalmic beta-blockers, cardiac glycosides, or anti-arrhythmic medications – cardiac sodium channel blockers and potassium channel blockers.[23] Body mass index (BMI, kg/m^2) was calculated from body weight measured with standard balance beam or digital scale calibrated with standard weights and height measured with a wall-mounted Harpenden stadiometer. Waist circumference was measured (cm). The presence of pacing during the recording was ascertained by examination of the PSG ECG recording. Cholesterol was measured an average of 3.4 years earlier during the MrOS baseline visit using a Roche COBAS Integra 800 automated analyzer that was calibrated daily (Roche Diagnostics Corp., Indianapolis, IN). Total cholesterol (mg/dl) was calculated as: high-density lipoprotein (mg/dl) + low-density lipoprotein (mg/dl) + 0.2*triglycerides (mg/dl). Cardiovascular disease (CVD) was

defined by history of myocardial infarction, coronary angioplasty, stroke and/or coronary artery bypass graft surgery by participant self-report of physician diagnoses.

STATISTICAL ANALYSIS

Participant characteristics were summarized as mean +/− SD or n (%) and were compared using Chi-square tests for categorical variables and t-test for continuous variables. HRV indices were expressed by quartile with frequency-based HRV indices (LF, HF, LF/HF) considered as primary predictors given generally accepted use as indices of sympathovagal balance. Secondary HRV measures considered include time domain MNN, STV and STV/LTV indices. Cox proportional hazard models were used to determine the risk of incident AF across HRV quartiles. A test of trend was performed across the quartiles to assess for monotonic relationships of HRV and atrial ectopy measurements and incident AF. Premature atrial contractions (PACs) were also examined given data implicating atrial ectopy as a harbinger of AF development [9]. Unadjusted models were performed as well as multivariable models adjusted for age, race, BMI (kg/m^2), waist circumference (cm), self-reported medical history including the following considered as individual covariates: [cardiovascular disease, heart failure, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD)], anti-arrhythmic/beta blocker/calcium channel blocker medications, total cholesterol, alcohol use, study site. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). P-values for trend are presented reflecting the trend of risk of incident AF across quartiles of HRV measure. Secondary analyses were conducted testing for the statistical interaction of SDB indices (AHI ≥ 15, OAHI ≥ 15, CAI ≥ 5) with HRV variables and stratification was performed. Interaction terms were considered significant if p<0.10. In order to assess robustness of analyses, we performed separate sensitivity analyses excluding: 1) participants with second or third degree atrioventricular block (to address confounding by conduction delay arrhythmia), 2) participants with less than 5 usable HRV epochs of data and 3) participants using positive airway pressure (PAP) therapy. All significance levels reported are two-sided and all analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

STUDY POPULATION

Of the 2350 participants, over the 8.0 ± 2.6 year follow-up period, incident adjudicated AF was observed in 269 (11.4%) subjects (Table 1). Of all participants 89.7% were Caucasian, the average age was 75.8± 5.3 years and overall, were non-obese: 27.1± 3.7 kg/m^2. A significant proportion had cardiovascular disease (26.1 %) and was taking cardiovascular medications (37.2%). These percentages were significantly higher in the incident AF group (40.3% and 57.3% for those without and with AF, respectively). Those with AF were also more likely to have hypertension. Overall, a median of 56 five-minute HRV epochs (range 1–135) were identified for analyses.

ELECTROPHSYIOLOGIC INDICES AND INCIDENCE OF ATRIAL FIBRILLATION

Proportional hazards assumptions were evaluated statistically and determined to be satisfied for all models. In multivariable adjusted analyses, those in the lowest LF quartile were 46%

more likely to develop AF compared to the reference group (quartile 4). Similarly, participants in the lowest LF/HF quartile had 46% higher risk of incident AF compared to the highest quartile. (Table 2) In the unadjusted analyses for the frequency domain HRV indices, lower LF and LF/HF were associated with increasing risk of incident AF (all p-trend=0.001), and the association remained statistically significant for HF and LF/HF in multivariable adjusted analyses (p-trend=0.043 and 0.021, respectively). For the time domain HRV measures, there was a significant relationship of increasing MNN, STV and STV/LTV and higher risk of AF (p-trend 0.011, 0.003 and 0.0001 respectively), however, in multivariable adjusted analyses significance persisted for STV/LTV only (p-trend= 0.028). (Table 3) A statistically significant relationship with a strong magnitude of association of premature atrial contractions and incident AF was observed with an approximate 3-fold increased risk of AF in the highest quartile compared to the reference quartile 1 (HR=2.99, 95% CI 1.94–4.62). Moreover, compared to Quartile 1, Quartiles 2 and 3 of premature atrial contractions were associated with a 2.2 fold (HR=2.19, 95% CI 1.31–3.43) and 2.5 fold (HR=2.50, 95% CI 1.62–3.87) increased risk of incident AF compared to the reference quartile. (Figure 2)

SECONDARY ANALYSES

Tests of interaction were used to analyze how SDB modified the relationship of HRV indices and incident AF. There was a trend towards a significant interaction between LF and SDB (defined as AHI 15) and a significant interaction of obstructive sleep apnea (defined as OAHI 15) and LF in relation to incident AF, p=0.06 and 0.045 respectively. In multivariable adjusted stratified analyses, a 35% increased risk of AF per 1 SD decrease in LF was observed in those with AHI 15 (1.35, 1.09–1.68) and OAHI 15 (1.34, 1.08–1.66), a finding not observed in those with AHI<15 (0.99, 0.83–1.18) or OAHI<15 (1.00, 0.84–1.20) (Figure 3). Similarly, a trend towards a statistically significant interaction was observed between HF and central sleep apnea (defined as CAI 5), p=0.06 with multivariable adjusted stratified analyses showing more pronounced relationships of increases in HF and increased AF in those with CAI 5 (2.12 per SD increment in HF, 1.17–3.85) compared to CAI<5 (1.11 per SD increment in HF, 0.97–1.28). There was no significant statistical interaction of PAC frequency and SDB indices relative to incident AF.

SENSITIVITY ANALYSES

After excluding 51 (2.2 %) men with second or third degree atrioventricular block, there were no substantive changes in the results. Separate analyses, excluding those participants using CPAP (n=20, 0.9%) also did not appreciably alter results. After excluding 160 (6.8%) studies with less than 5 epochs of usable HRV data, findings were strengthened in terms of magnitude of association and the trend of increasing AF across HF quartile remained statistically significant in multivariable adjusted analyses with 54% increased AF in the highest quartile (1.54, 1.06–2.24) when compared with the lowest quartile (p trend=0.010).

Discussion

In this multicenter, community-based cohort of older men, we observe that polysomnographic-based derived frequency domains of HRV predict increasing AF

incidence. A progressive reduction in LF/HF, i.e. a reflection of lower sympathetic to parasympathetic activity, was associated with increased adjudicated AF incidence over 8-year follow up after consideration of confounders such as obesity, cardiac disease and cardiac medications. Men in the lowest LF quartile (i.e. indicative of low level of sympathetic activation) had a 46% increased adjusted risk of AF compared to the highest LF quartile. Monotonic increases in time domain HRV indices, STV and STV/LTV, demonstrated significant associations with increased AF risk across increasing quartile. Additionally, increasing quartile of PACs per hour of sleep was associated with increased adjusted AF risk with a near 3-fold increased risk of AF in the highest compared to the lowest quartile. SDB indices of obstructive sleep apnea modified the relationship of LF and incident AF, i.e. a33% increased AF risk relative to reduction in LF in severe obstructive apnea; findings not observed in lesser apnea. This work addresses research priorities outlined in the Heart Rhythm Society Atrial Prevention guideline to examine SDB and polysomnographic determinants of AF development.[6]

Autonomic activity is increased in patients with SDB. It has been previously shown that alterations in autonomic regulation modulates SDB-related atrial arrhythmogenesis [5]. Heart rate variability (HRV) is a widely used tool to measure autonomic activity. Among the frequency dependent spectral variables, HF (0.15–0.40 Hz) is thought to reflect parasympathetic tone and the LF (0.04–0.15 Hz) provides combined information of the parasympathetic and the sympathetic nervous system [14]. However, we recognize that this may represent an oversimplification and may not accurately reflect all aspects of the two limbs of the autonomic nervous system, but rather tend to reflect the overall sympatho-vagal balance. PSG derived HRV presents an easily obtainable and analyzable source of continuous autonomic activity monitoring. As the raw data are already recorded, only further software based analysis is required with use of analytical techniques which are already well-established.

Previous work utilizing 24 hour-Holter monitoring in the Cardiovascular Health Study show that PAC count confers an additional risk for AF beyond traditional risk factors, i.e.[9] a median hourly PAC count at baseline was significantly higher in participants with incident AF (5.3 beats/hour) compared to without (1.8 beats/hour). These results are consistent with our findings of a relatively low threshold of PAC burden conferring increased AF risk. [9] The novelty of the current findings lies in identifying AF predictive value of PAC frequency from nocturnal ECG recordings as opposed to 24 hour continuous ECG monitoring. Our results suggest the possible utility of nocturnal PSG-derived electrophysiologic markers to verify PAC frequency as an AF risk without the requirement of longer duration ECG monitoring. As PACs in pulmonary veins can result in AF triggering and ablation of PACs may reduce AF recurrence [24], the ability of PSG-based ECG monitoring may play a role in identification of those most susceptible to target for AF prevention and treatment.

As the evidence for the link between SDB and AF (and other arrhythmias) is continuing to grow, we will require more robust and readily available tools to quantify and improve prediction of AF in SDB. PSG-derived HRV variables may provide an opportunity to allow for risk quantification and stratification, although not systematically examined in the current work. Use of these markers may provide an early warning for AF risk and possibly to tailor

effective treatment to mitigate risk in susceptible individuals. Normalization of these indices reflecting improvement of autonomic dysfunction may serve as a physiological marker of SDB treatment compliance and efficacy particularly as we currently rely on positive airway pressure machine derived proof of compliance with SDB therapy and symptom-based proof of efficacy. This, however, remains speculative and requires prospective confirmation. Separation of HRV indices based on sleep stage may also provide useful data as it relates to SDB. Alternatively, normalization of HRV and PAC metrics may predict long-term effectiveness of AF therapies.

Strengths of this study include its large sample size generalizable to healthy, community-dwelling older men (prone to develop AF); the prospective and longitudinal nature; the rigorous HRV analysis using standard methodology; use of SDB cutoffs relevant to current practice, careful consideration of confounding factors and multiple sensitivity analyses to exclude influence of overt conduction delay. The limitations are that this study is not generalizable to women or young men, infirmed older men or non-whites. The observational design precludes definitively excluding the possibility of residual confounding. Despite biologic plausibility, the observational design precludes ascertainment of definitive causal conclusions of sleep apnea-related HRV resulting in increased AF risk. Furthermore, other aspects of SDB-related pathophysiology such as altered cardiac substrate (e.g. atrial remodeling and scarring) [25] resulting in increased AF were not examined. Finally, while HRV analyses are a widely used tool in cardiology due to sound reproducibility, noninvasive nature, and data supporting these indices as a cardiac disease prognostic marker [26], limitations should be recognized including assumptions of heart rate, respiration and complexities of non-linear and sometimes reciprocal relationships of sympathetic and parasympathetic nerve activity [27].

In summary, a progressive reduction of a surrogate of sleep-related sympathovagal balance (LF/HF) gleaned from PSG-based ECG data represents an independent risk factor for AF development given preservation of point estimate strength after accounting for a multitude of confounders. These results suggest that enhanced vagal tone detected by PSG-based electrophysiologic indices represents a potential forecasting AF biomarker. Furthermore, obstructive sleep apnea, a disorder accompanied by enhanced parasympathetic activity during the apneic and hypopneic events, appears to modulate the relationship of LF/HF and incident AF.

This is consistent with the biologic basis of obstructive sleep apnea-related autonomic alterations resulting in AF possibly via electrical remodeling. Frequency of PACs during 24-hour continuous ECG monitoringhas been linked to increased AF and mortality. Similarly, we observe association of PAC frequency identified by limited PSG-based ECG monitoring during sleep and incident AF. These findings have potential implications in terms of utilizing PSG-based physiologic signatures for risk stratification and AF preventative or therapeutic targets thereby providing basis for further study. Future investigation should assess whether subtle cardiac conduction abnormalities may distort the expected association of electrophysiologic biomarkers of sympathetic/parasympathetic balance and AF development. The contribution of sleep state influences with inherent autonomic characteristics also represents an area of future investigation. The impact of state- or stage-

specific alterations in PSG ECG-based biomarker autonomic physiology has been described [28]; however, these inter-relationships as it pertains to AF risk should also be investigated. Furthermore, it remains to be seen whether reversal of SDB pathophysiology with standard therapy, i.e. positive airway pressure, or otherwise, attenuates SDB-modulated alterations in HRV parameters and alters outcome as it relates to incident AF risk.

Perspectives

Competency in Medical Knowledge

In the current era of enhanced recognition of the importance of sleep disordered breathing, the conduct of sleep studies, particularly home sleep apnea testing (the latter unlike in-laboratory sleep studies not standardly conducted with ECG monitoring), are in parallel increasing and result in over 1 million sleep studies performed annually. Continuous ECG monitoring conducted as part of sleep study monitoring provides a unique opportunity to leverage embedded physiologic signatures that predict adverse outcomes such as atrial fibrillation. The current work identifies heart rate variability measures of autonomic function and atrial ectopy as a surrogate of pulmonary vein triggers as predictors of incident atrial fibrillation in a cohort of older men, the latter a group vulnerable to development of actionable atrial fibrillation. Findings suggest the potential utility of standardly including the ECG signal as part of sleep apnea testing as a salient resource for atrial fibrillation risk stratification.

Translational Outlook

Further work is needed to identify specific heart rate variability or atrial ectopy thresholds which confer the greatest increased risk of atrial fibrillation development. While the current work provides the platform to pursue this investigation, findings require validation and extrapolation in independent data. Refinement of the influence of apnea related breathing disturbances and delineation of cardiac electrophysiologic data across sleep stage is also of interest. Future investigation should be focused on the impact of reversal of sleep disordered breathing-related autonomic physiology on alteration of heart rate variability and atrial ectopic parameters as it relates to atrial fibrillation risk.

Acknowledgments

Abbreviations List

AF　　Atrial fibrillation

AHI　　apnea hypopnea index

HF	high frequency power
HRV	heart rate variability
HSAT	home sleep apnea testing
LF	low frequency power
LTV	long term variability
PSG	polysomnography
STV	short term variability
SDB	sleep disordered breathing

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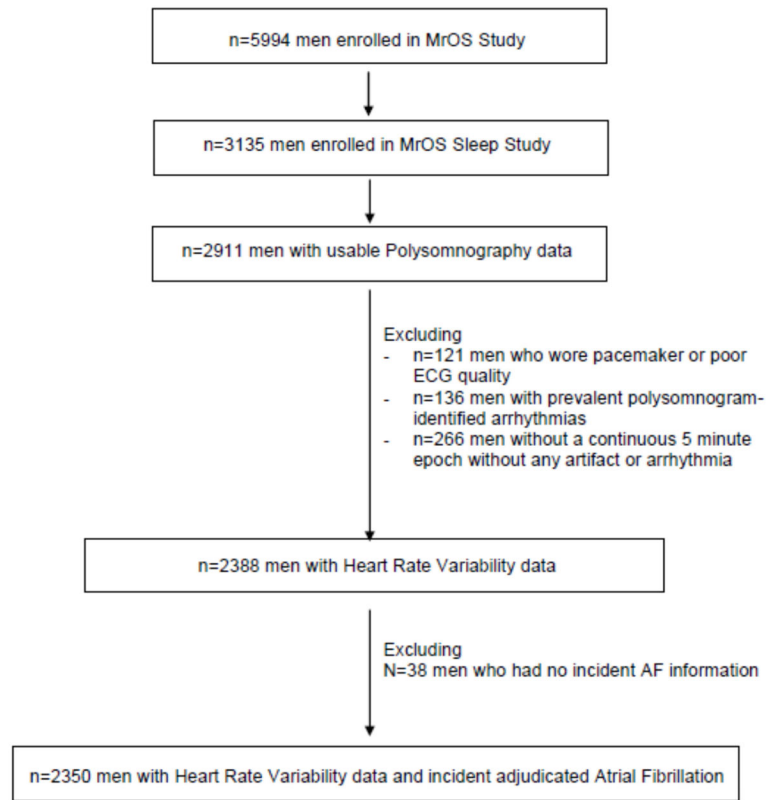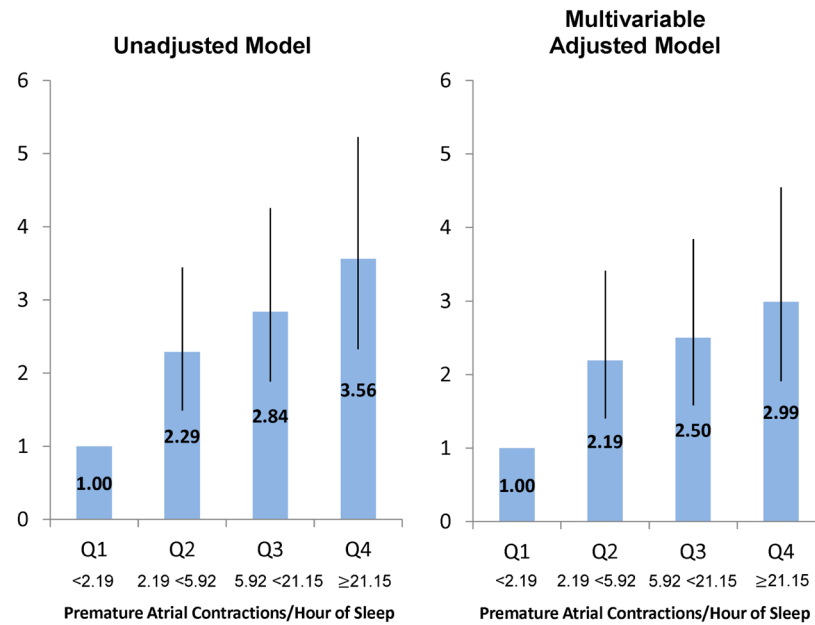
Figure 1.
Flow Diagram

Figure 2. Frequency of Atrial Ectopy as a Predictor of Incident Adjudicated Atrial Fibrillation*
*Hazard Ratios and 95% Confidence Intervals

In the adjusted model, a statistically significant association of premature atrial contractions and incident atrial fibrillation (AF) was observed with an approximate 3-fold increased risk of AF in the highest quartile compared to the reference quartile 1 (HR=2.99, 95% CI 1.94–4.62). Compared to Quartile 1, Quartiles 2 and 3 of premature atrial contractions were associated with a 2.2 fold (HR=2.19, 95% CI 1.31–3.43) and 2.5 fold (HR=2.50, 95% CI 1.62–3.87) increased risk of incident AF compared to the reference quartile.The adjusted model included the following covariates: 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.
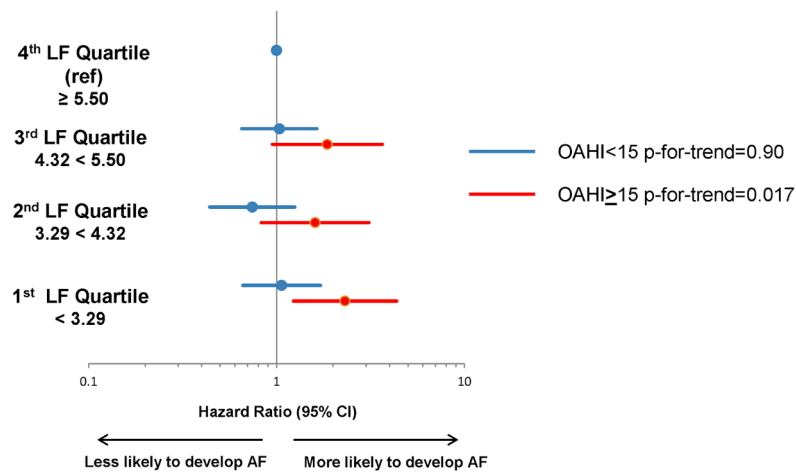
Figure 3. Low Frequency Power Heart Rate Variability by Obstructive Sleep Apnea Group
This dot represents Hazard Ratios depicted by dots and horizontal lines which reflect the confidence intervals. A 35% increased risk of atrial fibrillation (AF) per 1 SD decrease in low frequency (LF) power was observed in those an obstructive apnea hypopnea index (OAHI)>15 (1.34, 1.08–1.66), a finding not observed in those with an OAHI<15 (1.00, 0.84–1.20) The results reflect the statistical model adjusted for the following covariates: 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. *Key.* Obstructive apnea hypopnea index (OAHI)

Table 1

Baseline Characteristics, Overall and by Adjudicated Atrial Fibrillation Status

	Overall (n=2350)	Adjudicated Atrial Fibrillation (n=269)	No Atrial Fibrillation Development (n=2081)	p-value
Subject Characteristics				
Age (years)	75.8 (5.3)	76.7 (5.1)	75.7 (5.4)	0.004
Race - Caucasian	89.7	95.9	89.0	0.0004
Body Mass Index (kg/m^2)	27.1 (3.7)	27.6 (3.9)	27.1 (3.6)	0.03
Waist Circumference (cm)	99.5 (10.7)	100.7 (11.0)	99.3 (10.7)	0.05
Cardiovascular Disease	26.1	40.3	24.3	<0.0001
Heart Failure	3.8	6.7	3.5	0.009
Hypertension	49.0	61.0	47.5	<0.0001
Chronic Obstructive Pulmonary Disease	5.0	3.4	5.2	0.19
Diabetes Mellitus	13.1	13.8	13.0	0.72
Use of Cardiovascular Medication	37.2	57.3	34.6	<0.0001
Pacemaker	0.6	0.7	0.5	0.65
Current Smoker	2.0	2.2	2.0	0.78
Alcohol Use (Past 12 months)	65.6	61.3	66.2	0.12
Total Cholesterol (mg/dl)	194.2 (33.7)	190.1 (31.6)	194.7 (34.0)	0.04
Electrocardiogram Indices				
Premature Atrial Contractions/Hour 5	54.3	68.8	52.5	<0.0001
MNN	1.01 (0.15)	1.04 (0.16)	1.01 (0.14)	0.0008
STV	0.02 (0.02)	0.03 (0.02)	0.02 (0.02)	0.03
LTV	0.07 (0.03)	0.07 (0.03)	0.07 (0.03)	0.43
STV/LTV	0.39 (0.21)	0.43 (0.21)	0.39 (0.21)	0.004
LF	4.48 (1.71)	4.15 (1.66)	4.52 (1.71)	0.0007
HF	0.93 (0.72)	1.02 (0.64)	0.92 (0.73)	0.02
LF/HF	11.5 (9.9)	9.8 (8.9)	11.8 (10.0)	0.0009

Participant characteristics are summarized as mean +/− SD or n (%) and compared using Chi-square tests for categorical variables and t-test for continuous variables.

Key. Mean (SD) for continuous variables and percentage for categorical variables presented.

MNN=Mean of normal to normal heart beats

STV=Short term variability from Poincare plot

LTV=Long term variability from Poincare plot

LF=Normalized low frequency power

HF=Normalized high frequency power

Table 2

Frequency Domain Heart Rate Variability Indices as Predictors of Incident Adjudicated Atrial Fibrillation

	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

Key. LF=Normalized low frequency power, HF=Normalized high frequency power

Table 3

Time Domain Heart Rate Variability Indices as Predictors of Incident Adjudicated Atrial Fibrillation

	MNN	STV	STV/LTV
Model 1			
Q1, n=587	ref	ref	ref
Q2, n=588	0.97 (0.68, 1.40)	1.10 (0.76, 1.58)	1.04 (0.71, 1.50)
Q3, n=588	1.13 (0.80, 1.61)	1.22 (0.86, 1.74)	1.29 (0.90, 1.84)
Q4, n=587	**1.48 (1.06, 2.07)**	**1.65 (1.17, 2.31)**	**1.89 (1.35, 2.65)**
p-trend	**0.011**	**0.003**	**0.0001**
Model 2			
Q1, n=587	REF	REF	REF
Q2, n=588	0.99 (0.68, 1.44)	1.00 (0.68, 1.45)	0.90 (0.61, 1.32)
Q3, n=588	1.02 (0.71, 1.49)	1.12 (0.78, 1.62)	1.12 (0.78, 1.62)
Q4, n=587	1.30 (0.91, 1.85)	1.36 (0.96, 1.93)	1.40 (0.98, 2.00)
p-trend	0.13	0.057	**0.028**

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

Key. MNN=Mean of normal to normal heart beats, STV=Short term variability from Poincare plot, LTV=Long term variability from Poincare plot