Obstructive Sleep Apnea and Cardiac Electrophysiologic Biomarkers of Sudden Cardiac Death

Study Protocol and Statistical Analysis Plan

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BACKGROUND

Ventricular tachyarrhythmias (VTA) are a major cause of sudden cardiac death which account for half of cardiac mortality affecting approximately 3 million individuals world-wide. In fact, rates of sudden cardiac death are in excess of the mortality accompanying breast, lung and colorectal cancer *combined*. Data suggest that 50-85% of sudden cardiac deaths are attributable to ventricular tachycardia or ventricular fibrillation. Obstructive sleep apnea (OSA), an entity characterized by repetitive episodic breathing cessation during sleep, represents a highly prevalent physiologic stressor afflicting upwards of 17% of the population. Emerging experimental data implicate OSA-related intermittent hypoxia, autonomic nervous system fluctuations and alterations in intrathoracic pressure on risk of cardiac arrhythmogenesis (***Figure 1, Appendix***). Similarly, data from epidemiologic studies— much of which has been generated by our group-- support a strong association of OSA and ventricular tachyarrhythmias (VTA). Accordingly, clinic-based studies show nocturnal predilection to increased sudden cardiac death in OSA compared to those without OSA. In stark contrast to other etiologies of cardiac mortality, the incidence of sudden cardiac death has only marginally reduced over the last decade. *Although, based upon compelling experimental mechanistic data and epidemiologic data, OSA represents a potential novel therapeutic target to reduce VTA-induced sudden cardiac death; this key area of investigation remains vastly understudied.* OSA has been associated with cardiac repolarization abnormalities and implicated in sudden cardiac death. A biologically plausible mechanism by which OSA exerts this lethality is by QT interval prolongation, a known marker of VTA leading to cardiac death. Congenital long QT syndrome (LQTS) is a familial arrhythmogenic disorder characterized by prolonged QT interval on the electrocardiogram and increased propensity for VTA. Preliminary data identify an association of the extent of severity of OSA and progressive prolongation of the corrected QT interval in LQTS.

We propose a study to serve as an initial step to overcome existing critical knowledge gaps, i.e. characterizing the influence of OSA on QT prolongation in LQTS as well as other more common clinical scenarios such as in acquired heart disease and arrhythmogenic drugs. Furthermore, given the complete lack of data on treatment effect, we plan to examine the impact of OSA treatment on QT prolongation and innovative T wave morphologic characteristics via an interventional study. Expected results will be of high impact given ability to generate pilot data which can serve as the foundation to be used to identify and inform future screening and treatment approaches for management and/or mitigation of VTA propensity. Data will also set the stage to identify key outcomes for OSA clinical trials in these vulnerable populations. Our team is uniquely poised to carry out the proposed research as we have assembled a team with clinical and research expertise in sleep disorders and cardiac electrophysiology with experience conducting clinical trials, epidemiologic studies and cardiac electrophysiologic signal processing and an already partially assembled cohort of patients with prolonged QT interval.

SPECIFIC AIMS

Aim 1. To examine the extent that OSA severity and degree of hypoxia are associated with QT interval prolongation and novel T wave morphologic assessments on serial hourly 12-lead ECG collected during overnight polysomnography and also corrected QT interval (QTc) from daytime 12-lead ECG in those predisposed to prolonged QT interval, i.e. those with 1) LQTS, 2) acquired heart disease and 3) arrhythmogenic drugs.

Hypothesis 1. We hypothesize that the extent of severity of OSA and degree of hypoxia (defined by the apnea hypopnea index and percentage of sleep time spent <90% respectively) will be associated

with QT interval prolongation and novel T wave morphologic assessments even after consideration of confounding factors including age, sex, race and body mass index. Exploratory analyses will examine the mediation of cardiac substrate (left ventricular ejection fraction) on these associations.

Aim 2. To investigate the effect of OSA treatment with 3-month continuous positive airway pressure (CPAP) on QT interval duration as well as novel biomarkers of T wave morphology observed on ECG data collected during overnight polysomnography and also QTc collected from daytime 12-lead ECG in those with LQTS.

Hypothesis 2. We postulate that 3-month treatment of OSA will reduce the QT interval and improve novel electrophysiologic markers of ventricular stability in patients who are vulnerable to VTA and sudden cardiac death.

SIGNIFICANCE

The application addresses an area of high significance, i.e. elucidation of OSA as a novel, biologically plausible therapeutic target to mitigate VTA and sudden cardiac death. This is an important area of investigation given the substantial contribution VTA confers to sudden cardiac death and unchanged incidence of sudden cardiac death over the last decade underscoring the need to identify novel preventative targets. Data generated from the proposal will set the stage to advance scientific understanding of the impact of OSA as an exacerbating factor of cardiac electrophysiologic markers of lethality with the potential to inform public health policy to reduce sudden cardiac death. Results will lay the foundation to provide preliminary data to inform personalized medicine approaches and risk stratification to focus efforts on identification of OSA in those with QT prolongation and therefore vulnerable to VTA.

INNOVATION

The innovation of the proposal is multi-faceted including evaluation of not only standard QT interval indices, but also cutting edge signal processing to examine cardiac electrophysiologic biomarkers predictive of lethal VTA. These innovative QT morphologic indices will also be examined in relation to OSA and hypoxia as likely physiologic triggers—an area that has yet to be investigated. Moreover, although there are scant clinical research data which support an association of OSA and QT prolongation, the impact of reversal of OSA pathophysiology with CPAP has yet to be investigated. The data culminating from our efforts will allow for generation of critical data to lay the foundation for clinical trials and extramural NIH R01 level funding.

PRELIMINARY DATA/FEASIBILITY

Epidemiologic Work from our Group Supporting Strong Magnitude of Association of Obstructive Sleep Apnea and Ventricular Tachyarrhythmia

Our group has generated data from an epidemiologic perspective which has demonstrated a strong association of OSA and ventricular cardiac arrhythmia. Specifically, population-based our work conducted in the Sleep Heart Health Study (n~600) and the Outcomes of Sleep Disorders in Older Men study (n~3K) support a strong association of OSA and nocturnal ventricular arrhythmia, i.e. complex ventricular ectopy and nonsustained ventricular tachycardia (NSVT), even after adjustment for confounding influences of underlying cardiovascular risk and obesity (***Figures 2-4, Appendix***). These findings translate to an impressive approximate 2-fold increased risk of ventricular arrhythmia in those with moderate to severe OSA. Moreover, utilizing a case crossover design, i.e. a design which is best used with a transient exposure and outcome, we have shown immediate temporal relationships of discrete apnea and hypopnea events and episodes of NSVT namely an 18-fold higher odds of NSVT in those periods of apnea or hypopnea compared to those without.

Experience Examining Cardiac Electrophysiological Indices and Obstructive Sleep Apnea

We identified a statistically significant association of polysomnogram (PSG)-based heart rate variability (HRV) autonomic function biomarkers and incident AF over and 8.0 ± 2.6 year follow up period and these associations were modified by measures of sleep disordered breathing in 2350 participants of a multi-center prospective study (Outcomes of Sleep Disorders in Older Men Study). Specifically, we observed that a 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) and that 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) (**Figures 5, Appendix**). These findings indicated that sleep-related reduced sympathovagal balance (LF/HF) and increased atrial ectopy are independently associated with future AF; a relationship modified by obstructive apnea.

Clinical Trial Experience/Recruitment and Retention

Our group has conducted several clinical trials and interventional studies utilizing CPAP involving collaboration with sleep medicine and cardiologists/electrophysiologists for which we have either met or exceeded recruitment goals and have had expected retention (drop out range: 10-20%). (*NIH/NHLBI HL079114: Oxidative Stress in Sleep Apnea and Cardiac Disease, NHLBI 1RC2HL101417: Phase II Trial of Sleep Apnea Treatment to Reduce Cardiovascular Morbidity, NHLBI R01 HL 109493: Elucidation of the Risk of Sleep Apnea in Atrial Fibrillation*).

METHODS

Participant Eligibility Criteria and Process for Recruitment

We plan to recruit 50 patients with QT prolongation as identified by ICD 10 426.82 from the Cleveland Clinic. At the Cleveland Clinic, we will utilize the Knowledge Program query tool and EResearch along with Dr. Peter Aziz's Registry: Cleveland Clinic internal registry for inherited arrhythmias (IRB: 16-1094) platforms to identify potential recruits. Those patients with congenital LQTS or QT prolongation related to acquired heart disease or arrhythmogenic drugs will be eligible. Approximately ~500 patients/year (42/month) with QT prolongation are evaluated at the Cleveland Clinic. Assuming 50% meet eligibility criteria and 50% of those are interested then ~n=125 patients will be recruited/year (n=16/month over 8 months). This translates into n~150 potential participants over the 8-month recruitment period which exceeds the n=50 cases required to meet sample size requirements.

<u>Inclusion Criteria:</u>

1) Clinical diagnosis of QT prolongation as described above, 2) Age 18-75 years, 3) Individuals able to participate in at least 2 overnight sleep and physiologic assessments over a 3 month period.

<u>Exclusion Criteria:</u> 1) Use of specific OSA treatments (CPAP, oral appliances), 2) Use of supplemental oxygen, 3) Severe chronic insomnia, 4) Circadian rhythm disorder (e.g. shift work sleep disorder, delayed or advanced sleep phase syndrome), 5) Insufficient sleep syndrome defined by reported sleep duration < 4 hrs, 4) Unstable medical conditions (e.g., new onset or changing angina, a myocardial infarction or congestive heart failure exacerbation documented within the previous 3 months, uncontrolled hypertension (BP>170/110), uncontrolled diabetes mellitus (HbA1c>9.0), uncontrolled hypo- or hyperthyroidism), 5) Psychiatric disorders which are inadequately treated, 6) Compromised competence, 7) Alcohol abuse (currently drinks >5 alcoholic drinks/day), 8) Inability to provide informed consent, 9) Illicit drug use over last 6 months. *Rationale for criteria:* Patients with sleep disorders will be excluded as other sleep disorders may influence arrhythmogenesis. Those on treatment for SDB will be excluded because treatment would preclude assessment of OSA pathophysiologic effects on QT biomarkers.

Those with unstable medical conditions or rapid or uncontrolled heart rate will be excluded due to safety reasons.

PROTOCOL

Potential participants will come to the Cleveland Clinic Clinical Research Unit (CRU) for informed consent, eligible participants will undergo a 12 lead electrocardiogram. If the participants is found to have long QT syndrome ($QT_c \geq$ 450 in men ad $\geq$ 470 in women) they will continue on in the study. If they are found to not have long QT syndrome they will exit the study. If continuing on in the study the participant will undergo a fasting venipuncture and blood pressure measurements.   The participant will then be shown how to use the portable sleep study hook-up and continuous 12-lead ECG monitoring to be monitored in the home setting. The sleep study and ECG monitors will be returned by a courier service the next morning.

Those participants who are identified to have OSA (apnea hypopnea index$\geq$5, estimate 50% of those recruited) on the portable sleep monitoring will be invited to wear CPAP for 2-3 months with a follow up visit with repeat portable polysomnographic and continuous electrophysiologic assessments and CRU visit for bloodwork and blood pressure.

DATA COLLECTION

Portable Polysomnography

The Embletta Gold ® is a battery-operated device that can sample data at a 1000 Hz sampling rate and store data at 200 Hz, with 1 GB of storage capacity allowing storage of data from up to 20-24 hrs of recording. The device contains the critical sensors which are recommended by the American Academy of Sleep Medicine as validated sensors for measuring OSA: nasal pressure/flow; thoracic and abdominal inductance plethysmography (effort); and finger pulse oximetry (oxygen saturation).
Relevant PSG Variables: A registered polysomnologist will score the sleep study data. Apneas will be classified as "central" or "obstructive" according to the absence or presence of respiratory effort respectively. Hypopneas will be scored as a 50% amplitude reduction in inductance or flow and associated 3% oxygen desaturation or arousal. Periodic breathing will be defined as airflow or inductance channels increasing and decreasing at least 50% from the maximum, in a cyclic waxing and waning or "sinusoidal" manner for a consecutive period of $\geq$10 min.

Continuous Overnight 12-lead ECG Monitoring

CardioDay Holter (GE) monitoring reads SEER 12 data and exports Holter data as individual 10 second, 12 lead reports up to six per minute, i.e. all recorded data. The monitor is capable of continuous 12-lead ECG monitoring with the ability to record up to 10 days with Bluetooth ® technology and 12-bit signal resolution with up to 1024 sampling rate.

ECG Sensor Application. This will be performed by a trained research coordinator at the visit in tandem with sleep monitor lead hook-up. Participants will be asked to remove clothing from the waist up to attach the sensors to the chest. Staff will ensure privacy by covering the participant with a sheet or gown. The staff will shave necessary areas on the chest prior to sensor application to ensure that the sensors stick closely to the skin and will provide the participant with the ECG monitor/holster/clip, leads, communicator and charger, electrodes and a handbook with simple pictorial/written educational instructions. A research coordinator will be available by phone 24-7 to address issues with device malfunction, lead placement and replacement of equipment. ECG quality grade data will be collected: (excellent: >90% of ECG data without artifact, good: 70-90% without artifact, fair: 50-70% without artifact, poor <50% artifact free).
Relevant ECG Variables. Standard average QT interval measures will be obtained with eventual ability to

examine peri-apneic and peri-hypopneic alterations in QT interval. Novel QT morphologic assessments will be made with the GE compatible platform described below.

Novel QT analysis platform

An analysis system which enables biopharmaceutical companies to analyze detailed morphology of the electrocardiography (ECG) T-wave (QT Guard Plus™, eResearchTechnology, Inc.). The system identifies and quantifies characteristic changes in the shape of the T-wave found in drugs that produce Torsades de Pointes (TdP), the latter a potentially lethal tachyarrhythmia. QT Guard Plus imports individual 10 second, 12 lead reports for analysis and parameter extraction, i.e. T wave shape measures with the capability to extract other electrophysiologic signatures as well.

Resting Blood Pressure

BP will be measured after the participant has been sitting quietly for at least 5 minutes following standardized guidelines using a calibrated sphygmomanometer. Cuff size will be determined by measuring the circumference of the upper arm, measured at the midpoint and identifying the appropriate bladder size from a standard chart. Measurements will be repeated three times and recorded.

Fasting Venipuncture

Phlebotomy (40cc) will be performed the morning of the baseline and follow-up visits using standard techniques by trained research staff following written procedures (e.g., pre-labeled bar coded tubes, minimizing trauma, etc.). The sample will be divided into tubes for the varied analyses (20 mL clot for serum, 20 mL EDTA). Clots will be centrifuged and the serum removed within 1 hr of venipuncture. Plasma from EDTA samples will be stored for future DNA analysis. Assays will be stored in dedicated, alarmed freezers at -80°C in the CRU Core Lab and transferred to designated space in the Pathology and Laboratory Medicine Institute.

Morning blood work to examine the association of electrolytes in relation to QT interval duration and stability upon follow up after use of CPAP. With collateral funding, bloodwork will allow for examination of markers of systemic inflammation which may serve as intermediary pathways for cardiac electrophysiologic biomarkers of VTA in OSA.

Continuous Positive Airway Pressure Intervention

Subjects randomized to CPAP will be provided with an Autopap REMstar device (Philips-Respironics, Inc, Murrysville, PA) with integrated humidifier, set at a pressure range of 4-20 cm H_2O, with auto-titration according to the device's algorithm for detecting airflow limitation which provided wireless transmission of usage information to our research team.

STATISTICAL ANALYTIC PLAN

EXPOSURES: *Primary:* 1) OSA defined by AHI, i.e. number of apneas + hypopneas/hour of sleep. *Secondary:* 1) Hypoxia: % sleep time with SaO2 < 90%, 2) Central Sleep Apnea [central apneas/hour of sleep, Central Apnea Index (CAI)], 3) Periodic Breathing (Aims 1 and 2)

OUTCOME: 1) Corrected QT interval (ms) (primary outcome), 2) Quantitated T wave morphology via QT Guard software (ms) (secondary outcome) (Aims 1 and 2)

COVARIATES: Age, sex, race, body mass index (BMI, kg/m^2), anti-arrhythmic/beta blocker/calcium channel blocker/ACE inhibitor/angiotensin receptor blocker/antipsychotic medications, BP, diabetes mellitus, left ventricular ejection fraction (if echocardiographic data available).

Analytic Method by Aim.

Aim 1. Quantify the extent that OSA and hypoxia are associated with corrected QT interval duration. This aim will be addressed by fitting linear regression models and separately analyzing each OSA variable (primary variable: AHI) to obtain a beta estimate and standard error per 1-unit increase in the OSA exposure. Non-linear effects between OSA and QT duration will be assessed using restricted cubic splines. Knots for the spline will be based on the OSA threshold at which QT prolongation risk increases. Unadjusted and hierarchical adjusted models will be performed using the covariates listed above. The secondary exposure variables (e.g. hypoxia, central apnea index) will be considered in separate models. The secondary outcome of quantitated T wave morphology will be evaluated in separate analyses per the approach described above.

Aim 2. Examine the effect of OSA (AHI≥5) treatment for 3 months on QT interval duration.

For this subgroup of OSA (AHI≥5, estimated to be 50% of n=50) and we will perform t-tests to compare pre- and post- treatment mean outcome (Primary outcome: QT duration) and also novel quantitated T wave morphologic measures. For either outcome for which a departure in normality is found (based on the Shapiro-Wilk test) but a transformation of the outcome can not be found to adequately address the issue, we will use the Wilcoxon signed rank sum test to detect a difference in the distribution of the pre- and post- responses. This assessment is not intended to be confirmatory, but rather to provide estimates of variability and effect sizes to inform future studies/randomized trials. Linear regression models will then be developed to QT interval duration at the 3-month visit by conditioning on baseline QT interval duration, baseline OSA, and time from baseline to 3-month visit. Additional adjusted models will carefully consider the covariates list above.

POWER BY AIM.

Specific Aim 1. A sample size of 50 will be able to detect 0.59 standard deviations with 80% power (and 0.62 with 90% power), assuming a 2-sided alpha level of 0.05 which is sufficient for generation of pilot data.

Specific Aim 2. Using a two-sample t-test (2-sided 0.05 alpha-level) to test for a difference in mean variation between the SDB (AHI≥5) and no SDB groups, a sample size of 50 (25 with OSA and 25 without OSA) will detect mean differences within 0.46 standard deviations with 80% power and 0.53 standard deviations with 90% power.

Alternative/Pitfalls

1. Although we have experience with successful cross-institutional collaboration and recruitment, it is possible that recruitment efforts may not be successful with the approach as outlined via EResearch and the KP query tool. If this is the case, we will plan to pre-screen patients in electrophysiology clinics.
2. We will not have research-grade time-concordant echocardiography to assess as a covariate factor, however, it is anticipated that many of the patients will have clinical ECHO studies for which we will conduct data extraction.
3. Although there will be heterogeneity in the sample in terms of the etiology of QT prolongation, this will be a strength as albeit we will be somewhat limited in power, we will be able to examine subgroup effect sizes.

Timeline

Please refer to **Figure 7** for the timeline. The first 2-4 weeks will be dedicated to solidifying protocols, establishing database and personnel training. Recruitment will begin month 1 until month 8 (goal recruitment 7-8 participants per month) with collection of in-tandem sleep monitoring and continuous 12-lead ECG monitoring with blood work. In months 9-12 statistical analyses will be conducted with

preparation of abstracts (submitted to Heart Rhythm and American Thoracic Society meetings) as well as manuscripts entitled *"Association of Obstructive Sleep Apnea and Corrected QT interval and Novel T Wave Morphologic Characteristics"* and *"Impact of Continuous Positive Airway Pressure on Corrected QT interval and Novel T Wave Morphologic Characteristics"* and preparation of an R01 application.

Future Directions

The goals of the application are to overcome existing knowledge gaps in understanding the influence of OSA on cardiac electrophysiology, namely QT prolongation, which predisposes to VTA and cardiac death. The pilot data generated will be key in elucidating the impact of OSA on predisposing to cardiac vulnerability in those who are predisposed, i.e. have congenital or acquired QT interval prolongation. Data generated will provide important information on effect size of OSA treatment on QT interval prolongation which will inform future studies.

Relevance and Benefit to CTSC/Translational Research

The insights garnered from the proposed pilot work will be scalable and provide key interventional data to lead to a larger clinical trial. We will also use CRU resources for blood work blood pressure assessments and statistical support. The application has a high likelihood of success given the public health importance of examination sleep-lethal cardiac arrhymogenicity to identify novel preventative approaches in the context of a cogent biologic basis, limited existing clinical data contributing to a large existing knowledge gap and scientific experience of the investigators, thereby ideally positioning us for this critical translational opportunity to then take to the next level via application for NIH or American Heart Association funding.

Data Sharing

We plan to make available de-identified, non-sensitive, individual-level information on objective sleep characteristics, subjective sleep health and medical history (e.g. comorbid factors and medication use) and sociodemographics (e.g., age, gender education level). We will submit the data generated from the current proposal to the NIH funded National Sleep Research Resource (NSRR). The National Sleep Research Resource (NSRR) offers free web access to large collections of de-identified physiological signals and clinical data elements collected in well-characterized research cohorts and clinical trials. The NSRR is a public resource which provides opportunities for investigators to address critical scientific questions of interest.

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