Sleep characteristics that predict atrial fibrillation

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BACKGROUND The relationship between sleep disruption, independent of obstructive sleep apnea (OSA), and atrial fibrillation (AF) is unknown.

OBJECTIVE The purpose of this study was to determine whether poor sleep itself is a risk factor for AF.

METHODS We first performed an analysis of participants in the Health eHeart Study and validated those findings in the longitudinal Cardiovascular Health Study, including a subset of patients undergoing polysomnography. To determine whether the observed relationships readily translated to medical practice, we examined 2005–2009 data from the California Healthcare Cost and Utilization Project.

RESULTS Among 4553 Health eHeart participants, the 526 with AF exhibited more frequent nighttime awakening (odd ratio [OR] 1.47; 95% confidence interval [CI] 1.14–1.89; $P = .003$). In 5703 Cardiovascular Health Study participants followed for a median 11.6 years, frequent nighttime awakening predicted a 33% greater risk of AF (hazard ratio [HR] 1.33; 95% CI 1.17–1.51; $P < .001$). In patients with polysomnography (N = 1127), every standard deviation percentage decrease in rapid eye movement (REM) sleep was associated with a 18% higher risk of developing AF (HR 1.18; 95% CI 1.00–1.38; $P = .047$). Among 14,330,651 California residents followed for a median 3.9 years, an insomnia diagnosis predicted a 36% increased risk of new AF (HR 1.36; 95% CI 1.30–1.42; $P < .001$).

CONCLUSION Sleep disruption consistently predicted AF before and after adjustment for OSA and other potential confounders across several different populations. Sleep quality itself may be important in the pathogenesis of AF, potentially representing a novel target for prevention.

KEYWORDS Atrial fibrillation; Insomnia; Obstructive sleep apnea; Rapid eye movement (REM) sleep

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Introduction

There are several known risk factors for atrial fibrillation (AF),[1] but predicting its onset and identifying strategies for primary prevention remain difficult.[2] Obstructive sleep apnea (OSA) has been established as a risk factor for AF,[3] but the mechanism remains unclear. Although episodes of hypopnea and apnea may cause cardiopulmonary stress, induce inflammation, and contribute to cardiovascular disease, OSA also causes poor sleep.[4] Aspects of poor sleep, such as altered sleep duration, efficiency, and architecture, have been linked to other cardiovascular diseases.[5] Sleep disturbance in general is more common than OSA,[6] and because strategies to enhance sleep quality are different than those that focus on relieving airway obstruction,[7] it is important to investigate the relationship between sleep itself and AF.

One cross-sectional analysis demonstrated that those with prevalent AF had reduced sleep efficiency and reduced slow-wave sleep (also known as stage N3).[8] Furthermore, AF episodes follow a circadian variation,[9] and patients sometimes report that poor sleep can trigger an episode.[10] However, these studies were limited to patients who already had an AF diagnosis, so "effect–cause" remains a possibility—AF itself may impair sleep. Before considering methods to enhance sleep quality as a broadly relevant approach to prevent AF, the influence of sleep disturbance before disease onset must be determined. Therefore, we sought to determine whether poor sleep would predict an increased risk of developing AF independent of OSA.

Methods

We evaluated the sleep–AF relationship in 3 distinct datasets. First, we identified the characteristics of sleep that were associated with prevalent AF in the Health eHeart Study. Next, we used the Cardiovascular Health Study (CHS) to test whether the patterns of poor sleep identified in the Health eHeart Study would predict incident AF in a longitudinal cohort. We leveraged a subset of CHS with polysomnography (PSG) data to further validate our findings using objective measurements. Finally, to test for a sleep–AF association in clinical practice, we used the California Healthcare Cost and Utilization Project (HCUP) to assess a physician-coded diagnosis of insomnia as a predictor of incident AF. We adjusted for OSA using markers available in each dataset. Approval for the Health eHeart Study and permission to use de-identified data from CHS and HCUP was obtained from the University of California, San Francisco Institutional Review Board.

Health eHeart Study

To identify aspects of sleep associated with prevalent AF, we used the Health eHeart Study (www.health-eheartstudy.org), an Internet-based prospective cohort study that began enrolling interested adults age ≥18 years with an active e-mail address on March 8, 2013 (Supplementary Methods). Participants provided baseline demographic and medical information via online surveys during their initial "eVisit." Those who enrolled through February 21, 2016, and provided age, sex, AF status, and completed a sleep survey were included in this study.

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI).[11] Demographics and medical conditions, including prevalent AF and OSA, were determined by participant self-report. Self-reported AF in the Health eHeart Study has been previously validated by review of medical records of a subset (N = 42) of participants and was found to be 100% sensitive (exact 95% confidence interval [CI] 86–100) and 100% specific (exact 95% CI 80–100).[12]

The PSQI score, standard interpretation ("poor" sleep if score ≥5), component subscores, and individual questions were compared between participants with and without prevalent AF (Supplementary Methods). Sleep measures associated with prevalent AF with $P < .05$ for both the overall ordinal variable and test for trend were included together in a multivariable model.

Cardiovascular Health Study

CHS is a population-based prospective cohort study that has been described in detail elsewhere.[13] In brief, 5201 adults age ≥65 years were recruited in 1989–1990 from Medicare eligibility lists of 4 counties in the United States. An additional 687 African Americans were recruited during 1992–1993. Participants underwent a comprehensive baseline examination, including surveys, vital sign measurements, and an electrocardiogram (ECG). Participants were followed by alternating semiannual clinic visits and phone calls until 1999 and phone calls every 6 months thereafter. Participants with prevalent AF were excluded, and the remaining patients were censored at the time of incident AF or death, or were administratively censored at the end of follow-up.

Sleep quality was ascertained during the baseline examination by 5 yes-or-no questions. OSA status was determined by the affirmative answer to either of 2 questions regarding snoring and apneic episodes (Supplementary Methods). Objective measures of sleep quality and OSA were available in a subset of CHS participants co-enrolled in the Sleep Heart Health Study who underwent at-home PSG during 1995–1998.[14] For this subset, the apnea hypopnea index (AHI), a continuous measure of OSA severity, was used to adjust for OSA. In a sensitivity analysis, we adjusted for the dichotomous presence of OSA, defined as AHI ≥5, a standard clinical cutoff.[4]

Prevalent AF was identified from baseline ECG or self-report of a physician's diagnosis.[15] Incident AF was identified by ECGs at follow-up study visits or by hospital discharge diagnosis codes supplemented with Medicare inpatient claims data.[16] The analysis in the PSG subset excluded any AF detected before the PSG study. Other covariates were obtained by standardized questionnaire and from study personnel (Supplementary Methods).

California HCUP

The California HCUP is a set of medical records databases that has been described in detail previously.[17] In brief, all