ARIC Manuscript Proposal # 1092

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SHHS Manuscript/Abstract Proposal Format

1. a. Full Title
Nocturia And Sleep-Disordered Breathing

1.b. Abbreviated title
Nocturia and OSA

2. Lead Author(s)
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3. Timeline [Target start and finish dates, assuming P&P approval and Co-ordinating Center Availability for analysis]:
Analysis could be initiated immediately, once CHS data becomes available

4. Rationale
Sleep-disordered breathing may lead to cardiovascular morbidity due to repetitive episodes of complete or partial upper airway obstruction (1). The mechanisms underlying such effects are complex and are attributed to increased cardiac transmural pressure generated during occluded breathing, hypoxemia, and increased sympathetic tone secondary to hypoxemia and arousals from sleep. However, severity of sleep-disordered breathing as measured by the apnea-hypopnea index (AHI) does not take into account the magnitude of increase in cardiac transmural pressures generated by swings in intra-thoracic pressure. But, all of these pathophysiological mechanisms – increased transmural pressure, hypoxemia, and arousals – stimulate the secretion of B-type natriuretic peptide (BNP)(2). Elevated levels of BNP can lead to nocturia, which, in turn, may be considered as globally representative of adverse cardio-respiratory interactions. Therefore, the central hypothesis of this proposal is that nocturia is a marker for adverse cardio-respiratory interactions and cardiovascular morbidity in patients with sleep-disordered breathing.

Moreover, although previous case series and reports have identified nocturia as a manifestation of sleep-disordered breathing (4-9), a comprehensive and systematic study of nocturia and the association between nocturia and sleep-disordered breathing has not been undertaken so far. Besides being representative of adverse cardio-respiratory interactions, nocturia per se may lead to adverse consequences. Nocturia has been reported to be the most bothersome of all urinary complaints and a frequently reported cause for sleep disturbance (10). Nocturia is associated with other important end-points such as poor health-related quality of life (11); falls in the elderly (12); as a reason for institutionalization of elderly patients by family members who report nocturnal disruptions due to repetitive awakenings from sleep (13); and even associated with all-cause mortality (14). Lastly, patients with nocturia, and as yet undiagnosed sleep-disordered breathing, may be presenting to urologists and urogynecologists with troublesome nocturia, and receive anti-diuretic hormone analogues (15, 16). A comprehensive assessment of the relationship between nocturia and sleep-disordered breathing is badly needed.
We propose to measure frequency of nocturia in a cross-sectional manner from the Sleep Heart Health Study (SHHS), and assess the association between nocturia, sleep-disordered breathing, hypertension, and prevalent cardiovascular disease.

5. Specific aims and associated hypotheses:

**Specific aim #1:** To determine the association between sleep-disordered breathing and nocturia.

**Hypothesis #1:** We hypothesize that sleep-disordered breathing is independently associated with self-reported frequency of nocturia in a large cohort of middle-aged and older individuals.

**Specific aim #2:** To determine the association between nocturia and cardiovascular morbidity.

**Hypothesis #2:** We hypothesize that self-reported frequency of nocturia is more strongly associated with risk for hypertension and prevalent cardiovascular disease than conventional measures of sleep-disordered breathing (AHI).

6. Data [variables, time window, source, inclusions/exclusions]

Occurrence and frequency of nocturia will be derived from the sleep habits. An assessment of the relationship between nocturia and patient demographics (age, BMI, gender), indexes of sleep-disordered breathing (AHI, arousal index, hypoxemia severity), medical history (Diabetes Mellitus), medications (diuretics), and social habits (caffeine consumption) will be performed. Simple logistic regression regression will be performed to identify significant variables. All variables, significant at P < 0.05 level, will be included as independent variables in multivariate logistic regression models with nocturia identified as the dependent variable (**Specific aim #1**). Models predicting various morbid cardiovascular endpoints such as hypertension will be constructed to compare the relative strength of AHI to nocturia frequency as independent risk factors after adjustment for covariates (**specific aim #2**).

7. References

16. FitzGerald MP, Mulligan M, Parthasarathy S. Association of obstructive sleep apnea and nocturia, and improvement of nocturia with continuous positive airways (CPAP) treatment of OSA. Am J Obstet Gynecol [In Press]