SHHS Manuscript Proposal
ARIC Manuscript Proposal #919S

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1. Title: Effect of elevated respiratory disturbance index (RDI) on plasma B-type natriuretic peptide (BNP) level.

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3. Timeline: Start of analysis on approval; preliminary draft to P&P 2/03

4. Rationale: B-type natriuretic peptide (BNP) is a peptide hormone secreted by the cardiac ventricles in response to increased wall stress. Plasma levels are elevated in individuals with left ventricular (LV) hypertrophy, asymptomatic left ventricular dysfunction, and overt heart failure.[1] Recently, considerable interest has developed in using these plasma peptides as serologic markers to identify the presence of LV dysfunction. Large community-based studies have demonstated that age and gender are significant predictors of elevated BNP levels.[2] The physiologic basis of these differences is not well-understood, although the age-related difference may reflect the higher prevalence of subclinical hypertension or cardiac disease or elevated RDI observed in older individuals. Obstructive sleep apnea (OSA) is associated with large negative swings in intrathoracic pressure, causing recurrent acute increases in LV transmural pressure. We hypothesize that this effect will be reflected in higher levels to plasma BNP. The purpose of this analysis is to assess the relation of RDI to plasma BNP levels, adjusting for other known covariates of BNP, including age, gender, blood pressure, and obesity.

5. Hypothesis: Higher RDI is associated with higher plasma BNP, and may contribute to the age-related increase in plasma BNP.

6. Data: The data to be used in this analysis include RDI from SHHS1 and both ANP and BNP levels measured in the SHHS participants from the FHS sixth offspring examination cycle (1995 to 1998). Covariate data will include age, gender, BMI, blood pressure as well as history of congestive heart failure. The source of data will be the Coordinating Center for SHHS data, the Framingham Study for ANP and BNP measures.

7. Type of Study: Secondary Study

8. Type of Publication: Journal Article
Target Journal: Sleep

9. Analysis Responsibility: Local

10. Introduction:

B-type natriuretic peptide (BNP) is a peptide hormone secreted by the cardiac ventricles in response to increased wall stress. Plasma levels are elevated in individuals with LV hypertrophy, asymptomatic LV dysfunction, and overt heart failure. BNP has also been shown to be elevated in patients with isolated diastolic dysfunction.[3] BNP synthesis is stimulated by increases in LV filling pressures and afterload. It is felt to be superior to atrial natriuretic peptide (ANP) as a diagnostic and prognostic marker in heart failure because of its longer half-life in vivo and its greater stability in vitro.[4] BNP levels are usually much lower than ANP levels; however, in pathological conditions affecting the ventricles, BNP may rise by several orders of magnitude, surpassing levels of ANP.[3]

BNP appears to be a useful diagnostic and prognostic marker in patients with known congestive heart failure (CHF). Although a recent paper from the Framingham Heart study demonstrated that both BNP and ANP performed poorly as initial screening tests for LV hypertrophy or LV dysfunction in the community, subjects with increased LV mass did have a higher mean BNP level compared to those without LV hypertrophy.[5]

A subsequent study on a healthy reference sample of 911 individuals from the Framingham cohort established reference normal limits based on age and gender.[2] Interestingly, older age and female status were significantly associated with higher BNP levels. The physiologic basis for the sex-related differences is unclear, although the stimulatory effect of female sex hormones on natriuretic peptide gene expression has been proposed.[6] The observation of higher natriuretic peptide levels with increasing age is striking, with BNP levels nearly doubling from age group 20-49 years to age 70 + for both men and women.[2] This finding is consistent with prior studies.[7,8] Of particular importance to the proposed analysis is the inverse association of BNP with body mass index (BMI), thought to reflect metabolism of BNP by adipose tissue.

One potential explanation for the age-related difference may be the effect of subclinical elevations in RDI observed in older individuals. ANP levels have been shown to be elevated in individuals with obstructive sleep apnea compared to controls.[9] This elevation is thought to reflect the increased cardiac volume load during obstructive events. Nasal CPAP therapy has been shown to decrease plasma levels of ANP in both obstructive and central sleep apnea patients.[10,11] We hypothesize that the elevated RDI observed in older individuals may explain, in part, the age-related increase in plasma BNP. Moreover, elevated BNP may identify a subset of subjects with OSA at increased risk of developing LV dysfunction.

11. Brief Analysis Plan:

Multivariable regression modeling will be used to assess the impact of RDI on plasma BNP levels. Because of the marked sex difference in BNP level, separate models will be constructed for men and women. Additional covariates age, BMI, and systolic and diastolic blood pressure will be assessed.

12. Summary Section:

The proposed study will analyze the relation of RDI to plasma BNP levels and determine the extent to which age-related elevations in plasma BNP level are explained by RDI.

13. References:

1. Daly C. et al. Natriuretic peptides in the diagnosis of heart disease – First among equals? *Int J Cardio* 2002; 84:107-113.
2. Wang TJ. et al. Impact of Age and Sex on Plasma Natriuretic Peptide Levels in Healthy Adults. *Am J Cardio* Aug 2002; 90:254-258.
3. Lang CC. et al. Increased levels of brain natriuretic peptide in patients with isolated diastolic dysfunction. *Am Heart J* 1994; 127:1653-1656.
4. Buckley MG. et al. Prolonged stability of BNP: importance for non-invasive assessment of cardiac function in clinical practice. *Clin Sci* 1998; 95:235-239.
5. Vasan RS. et al. Plasma Natriuretic Peptides for Community Screening for Left Ventricular Hypertrophy and Systolic Dysfunction: The Framingham Heart Study. *JAMA* Sept 2002; 288(10):1252-1259.
6. Hong M. et al. Estradiol, progesterone and testosterone exposures affect the atrial natriuretic peptide gene expression in vivo in rats. *Biol Chem Hoppe Seyler* 1992; 373:213-218.
7. Waku S. et al. Significance of brain natriuretic peptide measurement as a diagnostic indicator of cardiac function. *Methods Inf Med* 2000; 39:249-253.
8. Ohashi M. et al. High plasma concentrations of human atrial natriuretic polypeptide in aged men. *J Clin Endocrinol Metab* 1987; 64:81-85.
9. Maillard D. et al. Pressure-Heart Rate Responses to α-Adrenergic Stimulation and Hormonal Regulation in Normotensive Patients With Obstructive Sleep Apnea. *Am J Hyperten* 1997; 10:24-31.
10. Ehlenz K. et al. Reduction of nocturnal diuresis and natriuresis during treatment of obstructive sleep apnea (OSA) with nasal continuous positive airway pressure (nCPAP) correlates to cGMP excretion. *Med Klin* Jun 1991; 86(6):294-296.
11. Tkacova R. et al. Effect of Continous Positive Airway Pressure on Mitral Regurgitant Fraction and Atrial Natriuretic Peptide in Patients With Heart Failure. *J Am Coll Cardio* 1997; 30:739-745.