Obstructive Sleep Apnea and Plasma Natriuretic Peptide Levels in a Community-Based Sample

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Introduction

OBSTRUCTIVE SLEEP APNEA-HYPOPNEA (OSAH) SYNDROME IS ASSOCIATED WITH AN ALTERED HEMODYNAMIC STATE, REFLECTING BOTH SYMPATHETIC nervous system activation and the mechanical effects of inspiration against an occluded upper airway.1 In experimental investigations, acute airway occlusion during sleep causes a significant elevation in left ventricular peak systolic pressure with an associated rise in left ventricular end-systolic volume, a fall in venous return, and a reduction in stroke volume.2 Recurrent hypoxia and arousals associated with apneic episodes are thought to contribute to enhanced adrenergic activity,3 as evidenced by higher levels of urinary catecholamines in patients with greater nocturnal desaturations.4 The effects of sympathetic nervous system activation in patients with OSAH include an acute rise in systemic blood pressure after apneic events as well as sustained elevations in diurnal blood pressure that further contribute to increased left ventricular afterload.2,5

The natriuretic peptides, N-terminal pro-atrial natriuretic peptide (NT-ANP) and B-type natriuretic peptide (BNP), are sensitive markers of cardiac hypertrophy, ventricular dysfunction, and elevated filling pressures.6 Elevated natriuretic peptides may be predictors of heart failure and other cardiovascular disease in asymptomatic individuals without heart failure and also may portend a poorer prognosis in individuals with asymptomatic or minimally symptomatic heart failure.7 Elevated levels of natriuretic peptides in association with obstructive sleep apnea would therefore support the contention that obstructive sleep apnea is a risk factor for the development of cardiac dysfunction.

The authors anticipate that alterations in cardiac hemodynamics associated with OSAH may be reflected in higher plasma natriuretic peptides levels. However, published studies of the effect of OSAH on plasma natriuretic peptide levels are conflicting. Regarding ANP, Ichiooka et al reported higher plasma ANP levels in OSAH patients compared with controls during sleep,8 and Krieger et al reported a correlation of mean plasma ANP level with hypoxemia and esophageal pressure swings in 9 subjects with severe OSAH.9 Treatment of OSAH with continuous positive airway pressure (CPAP) has been reported to lower plasma ANP levels.9-12 Other studies, however, have reported either no association between OSAH and plasma ANP14,15 or inverse relations16 between plasma ANP and the apnea-hypopnea index (AHI). Regarding BNP, Kita et al reported increases in BNP levels during sleep between 2 AM and 6 AM in patients with OSAH and reductions in BNP levels after effective CPAP treatment,17 whereas both Moller et al15 and Svatikova et al18 reported no difference in BNP levels in patients with OSAH either with or without CPAP treatment.

Study Objectives: We hypothesized that alterations in cardiac hemodynamics associated with obstructive sleep apnea-hypopnea (OSAH) would be reflected in higher natriuretic peptide levels. We examined the association of OSAH with natriuretic peptides in a community-based sample.

Design: Cross-sectional, retrospective, observational study.

Setting: Framingham Heart Study Offspring Cohort and Sleep Heart Health Study.

Participants: Community-based sample of 623 individuals.

Measurements: Full-montage home polysomnography was used to determine apnea-hypopnea index (AHI) and percentage of time with an oxyhemoglobin saturation <90% (PctLt90). Sensitive immunoradiometric assays were used to measure plasma B-type (BNP) and N-terminal pro-atrial natriuretic peptide (NT-ANP). Multivariable regression was used to examine the relations between natriuretic peptides and indicators of OSAH, adjusting for age, sex, body mass index, and clinical covariates.

Results: No statistically significant relations between OSAH indices and BNP were observed in the multivariable model. Compared with an AHI <5, relative levels of 1.20, 0.88, and 0.91 were observed for AHI categories 5-15, 15-30, >30 events per hour, respectively. For NT-ANP, no significant relations were seen with AHI in the multivariable model (relative levels of 0.98, 0.91, and 0.90). An inverse association was observed between NT-ANP and PctLt90 in age- and sex-adjusted models (relative levels of 0.93, 0.87, and 0.80), although this association became statistically non-significant after adjusting for body mass index.

Conclusion: Lack of association of natriuretic peptides with OSAH indices suggests that undiagnosed OSAH may not be associated with major alterations in left ventricular function, as reflected in morning natriuretic peptide levels.

Keywords: Sleep apnea syndromes, natriuretic peptides, cohort studies

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All of these studies, whether positive or negative, have been limited by relatively small sample sizes, possible referral bias, or inadequate adjustment for potential confounders, including obesity, which is positively associated with OSAH and inversely associated with plasma natriuretic peptide levels. In the present analysis, we examined retrospectively the association of OSAH to plasma natriuretic peptide levels in a large community-based sample to test the hypothesis that OSAH is positively associated with plasma natriuretic peptide levels after adjustment for potential confounders, including obesity.

METHODS

Of 5124 members of the Framingham Offspring Study, 3532 were attendees of the sixth examination cycle. Natriuretic peptides were measured in 3462 attendees. From the Offspring cohort, 699 underwent overnight polysomnography between 1995 and 1998 as part of the Sleep Heart Health Study. Median length of time between polysomnography and natriuretic peptide testing was 79 days (interquartile range 27-280). We excluded 76 participants for the following reasons: prevalent heart failure or left ventricular dysfunction (defined as either fractional shortening < 22% or left ventricular ejection fraction ≤ 40%; n = 60), serum creatinine greater than 2 mg/dL (n = 6), and missing covariate data (n = 10). The analysis was performed on the remaining 623 participants. All participants gave written informed consent; the protocol was approved by the Boston University Medical Center Institutional Review Board.

In-home polysomnography was performed as previously described. AHIs were defined as the number of apneas plus hypopneas associated with ≥ 3% oxygen desaturation per hour of sleep time. Apnea and hypopnea were defined as previously described. The percentage of time spent with arterial oxygen saturations less than 90% (PctLt90) was measured using finger-pulse oximetry (Nonin, Minneapolis, MN).

Both BNP and NT-ANP levels were measured using sensitive noncompetitive immunoradiometric assays (Shionogi), as previously described. The lower limits of detection were 4 pg/mL for BNP and 94 pmol/L for NT-ANP. The average interassay coefficients of variation were 12.2% for BNP and 12.7% for NT-ANP. All natriuretic peptides were measured from fasting blood samples collected between 8 and 9 AM. Covariates, measured at the Framingham Heart Study clinic visit, included age, body mass index (BMI), systolic blood pressure, use of antihypertensive therapy, diabetes (fasting blood sugar ≥ 126 or use of hypoglycemic agent), atrial fibrillation, and myocardial infarction.

Multivariable regression was used to examine the relations of natriuretic peptides to two indicators of OSAH: AHI and PctLt90. Natriuretic peptides were logarithmically transformed to normalize their distributions. AHI was treated as a log-transformed continuous variable (ln[AHI+1]) as well as a categorical variable, using commonly used clinical thresholds (0-5, 5-15, 15-30, ≥ 30). PctLt90 was treated as a categorical variable, using approximate quartiles of the distribution, with clustering of zero values in lowest category: group 1 (n = 178), group 2 (0.004–0.182; median = 0.063; n = 144), group 3 (0.183–1.15; median = 0.47; n = 151), group 4 (1.19–91.8; median = 4.52; n = 150). Because of the wide distribution of values in the upper quarter, the analyses were repeated with this group divided in half: group 4A (1.19–4.52; median = 2.25; n = 75) and group 4B (4.52–91.8; median = 11.8; n = 75).

Tobit regression models (SAS LIFE-REG procedure [Version 8.2, SAS Institute, Cary, NC]) were used because of the left censoring of the peptide distributions. The distribution for BNP (and, to a lesser extent, ANP) in our sample is left censored because values less than the lower detection (censoring) limit are reported as equal to the lower detection limit. To analyze such data, we used the Tobit model, which is a regression model for left-censored data that assumes a normally distributed error term and that estimates model parameters by maximum likelihood. This approach simultaneously uses information from the censored fraction as well as the linear relation with covariates among noncensored values.

We examined regression models in a hierarchical fashion: (a) age- and sex-adjusted; (b) age-, sex-, and BMI-adjusted; and (c) multivariable-adjusted. Covariates in the multivariable models included age, sex, BMI, diabetes, systolic blood pressure, use of antihypertensive therapy, atrial fibrillation, and myocardial infarction. In secondary analyses, we evaluated whether the relation of AHIs and PctLt90 to natriuretic peptides varied according to sex or obesity (defined as BMI ≥ 30) by incorporating interaction terms in multivariable models. Both AHI and PctLt90 were incorporated into these models as categorical variables, as described above. All analyses were performed using SAS 8.1 (SAS Procedures Guide, Version 8. 1999.). A 2-sided p value < .05 was considered statistically significant.

RESULTS

The baseline characteristics of our sample, stratified by AHI clinical categories, are shown in Table 1. Median AHI was similar to estimates obtained from other community-based samples. Plasma BNP was not significantly associated with either AHI or with PctLt90 in any of the models (Table 2). Similarly, plasma NT-ANP was not significantly associated with AHI in any of the models. Plasma NT-ANP was inversely related to PctLt90 in age- and sex-adjusted models, although these associations were attenuated by adjustment for BMI (Table 3). An inverse relation between PctLt90 and plasma NT-ANP observed in the fully adjusted model was of borderline significance. When the upper quarter of PctLt90 was split in half, no statistically significant relations with either BNP or NT-ANP was observed (p value for multivariable model: BNP p = .10; NT-ANP p = .11). When the multivariable models were repeated using AHI as a logarithmically transformed continuous variable (ln[AHI+1]), the association with natriuretic peptide levels remained nonsignificant (Table 4). Parameter estimates and p values for covariate data are provided (Table 4).

Secondary Analyses

There was no significant effect modification by sex (p value for interaction term: BNP p = .35; NT-ANP p = .80) or by obesity (BNP p = .30; NT-ANP p = .48). Given the overall lack of association of OSAH indices with plasma natriuretic peptide levels in our sample, we evaluated our statistical power to detect such a relation. This study had at least an 80% power (at α [.2-sided] = .05) to detect an increase in the proportion of variance (R²) in natriuretic peptide measures explained by the addition of AHI or PctLt90 to the regression models as small as 1.4% for log BNP and 1.2% for log NT-ANP.
In this large community-based sample, OSAH was not significantly related to plasma natriuretic peptide levels in multivariable models. No statistically significant relations between OSAH and plasma BNP levels were observed in any of the models evaluated. For plasma NT-ANP, no association was seen with AHI, but an inverse association was observed with PctLt90 in age- and sex-adjusted models. This inverse relation, however, became statistically nonsignificant after adjusting for BMI and was of borderline statistical significance in the fully adjusted model. Rather than reflecting a true inverse relation, this finding may be a chance association or may reflect residual confounding by adiposity, which is associated with lower natriuretic peptide levels and is imperfectly measured by BMI. Repeating the analysis after splitting in half the upper quarter of PctLt90 again demonstrated no significant relation between PctLt90 and natriuretic peptide levels.

Obesity is a well-recognized risk factor for OSAH, as has been demonstrated in many populations, including the Sleep Heart Health Study cohort. Obesity has also been associated with reduced plasma natriuretic peptide levels in individuals without heart failure, thought to be a result of clearance receptors found abundantly on adipocytes. In our multivariable analyses, natriuretic peptide levels were positively associated with age and female sex and negatively associated with BMI, as expected based on prior literature. The association of OSAH with obesity might bias the analysis toward an inverse association. Even after adjustment for obesity, however, the expected association of OSAH with higher natriuretic peptide levels was not observed. The lack of association, even in the subset of 54 subjects with severe OSAH (AHI ≥ 30), a sample much larger than most previous studies of this topic, suggests that a true positive association does not exist.

The findings of this study support the prior observational literature that demonstrates no positive association between OSAH and natriuretic peptide levels and suggest that the reported association between natriuretic peptide levels and OSAH in clinic-based samples may reflect selection bias or confounding by covariates, such as diabetes, atrial fibrillation, or use of antihypertensive therapy. Prior reports of a reduction in plasma natriuretic peptide levels after treatment of OSAH with CPAP may simply reflect the beneficial effect of CPAP on left ventricular loading conditions, independent of its effects on OSAH. Alternatively, subjects with OSAH identified on the basis of population screening may differ physiologically from those presenting for evaluation in the clinical setting, although such differences have not been clearly demonstrated.

Our sample differs from prior case series primarily in a lower prevalence of atrial fibrillation, with 3% of our subjects reporting this condition, compared with 5% to 7% in previous studies of OSAH subjects. The prevalence of atrial fibrillation is also greater in OSAH subjects (7% vs. 3%) compared with community-based subjects (6% vs. 3%) without OSAH. This difference may reflect the beneficial effect of CPAP on left ventricular loading conditions, independent of its effects on OSAH. Alternatively, subjects with OSAH identified on the basis of population screening may differ physiologically from those presenting for evaluation in the clinical setting, although such differences have not been clearly demonstrated.

Table 2—Tobit Regression Models of Plasma BNP With AHI and Percentage Of Time < 90% Oxymembrin Saturation*

<table>
<thead>
<tr>
<th>AHI</th>
<th>Age &amp; Sex-adjusted</th>
<th>Age, Sex, &amp; BMI-adjusted</th>
<th>Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative level</td>
<td>95% CI</td>
<td>p value</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>Referent</td>
<td>Referent</td>
<td>.12</td>
</tr>
<tr>
<td>5 ≤ and &lt; 15</td>
<td>1.11</td>
<td>0.88, 1.39</td>
<td>1.16</td>
</tr>
<tr>
<td>15 ≤ and &lt; 30</td>
<td>0.85</td>
<td>0.64, 1.12</td>
<td>0.91</td>
</tr>
<tr>
<td>≥ 30</td>
<td>0.78</td>
<td>0.54, 1.13</td>
<td>0.85</td>
</tr>
<tr>
<td>Time with saturations &lt; 90%, %</td>
<td>.13</td>
<td>.27</td>
<td>.08</td>
</tr>
<tr>
<td>0</td>
<td>Referent</td>
<td>Referent</td>
<td>1.03</td>
</tr>
<tr>
<td>0.004 – 0.182</td>
<td>1.01</td>
<td>0.77, 1.31</td>
<td>1.03</td>
</tr>
<tr>
<td>0.183 – 1.15</td>
<td>1.03</td>
<td>0.79, 1.34</td>
<td>1.07</td>
</tr>
<tr>
<td>1.19 – 9.18</td>
<td>0.76</td>
<td>0.58, 1.01</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*Relative level is derived by exponentiating ß, the estimated regression coefficient. The 95% confidence interval (CI) is derived by exponentiating (ß ± 1.96 × SE), where SE is the estimated standard error of ß.

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Table 3—Tobit regression models of plasma NT-ANP with AHI and Percentage of Time Spent < 90% Oxyhemoglobin Saturation

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Parameter estimate (standard error)</th>
<th>p value</th>
<th>Parameter estimate (standard error)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln [AHI+1]</td>
<td>-0.03 (0.06)</td>
<td>.57</td>
<td>-0.05 (0.03)</td>
<td>.08</td>
</tr>
<tr>
<td>Age</td>
<td>0.04 (0.01)</td>
<td>&lt;.0001</td>
<td>0.03 (0.003)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.34 (0.10)</td>
<td>.0008</td>
<td>0.21 (0.04)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.02 (0.01)</td>
<td>.14</td>
<td>-0.01 (0.005)</td>
<td>.005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.11 (0.18)</td>
<td>.52</td>
<td>-0.19 (0.08)</td>
<td>.01</td>
</tr>
<tr>
<td>Prevalent atrial fibrillation</td>
<td>1.20 (0.32)</td>
<td>.0001</td>
<td>0.62 (0.14)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Prevalent myocardial infarction</td>
<td>0.65 (0.33)</td>
<td>.05</td>
<td>0.17 (0.15)</td>
<td>.24</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-0.002 (0.003)</td>
<td>.45</td>
<td>0.001 (0.001)</td>
<td>.49</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>0.08 (0.12)</td>
<td>.48</td>
<td>0.11 (0.05)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Table 4—Parameter Estimates and p Values for Multivariable Models

<table>
<thead>
<tr>
<th>Covariate</th>
<th>BNP model</th>
<th>NT-ANP model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative level</td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>AHI &lt; 5</td>
<td>.06</td>
<td>.43</td>
</tr>
<tr>
<td>5 ≤ and &lt; 15</td>
<td>.94</td>
<td>.98</td>
</tr>
<tr>
<td>15 ≤ and &lt; 30</td>
<td>.88</td>
<td>.94</td>
</tr>
<tr>
<td>≥ 30</td>
<td>.82</td>
<td>.89</td>
</tr>
<tr>
<td>Time with saturations &lt; 90%, %</td>
<td>.004</td>
<td>.13</td>
</tr>
<tr>
<td>0</td>
<td>.93</td>
<td>.95</td>
</tr>
<tr>
<td>0.004 – 0.182</td>
<td>.87</td>
<td>.91</td>
</tr>
<tr>
<td>0.183 – 1.15</td>
<td>.80</td>
<td>.85</td>
</tr>
</tbody>
</table>

Although this analysis is retrospective, it takes advantage of natriuretic peptide data collected by the Framingham Heart Study in a uniform standardized fashion for other analyses. All natriuretic peptides were measured from fasting blood samples collected between 8 and 9 AM. NT-ANP was measured preferentially because of its longer half-life relative to ANP. The half-life of BNP is approximately 22 minutes.

Both NT-ANP and BNP were measured, given their slightly different secretion profiles and stimuli for secretion. ANP is stored in atrial myocyte granules and is secreted in response to atrial stretch. In OSAH, ANP is released immediately with changes in intrathoracic pressure and oxygen saturation, both of which modify atrial distending pressure. BNP is secreted primarily by the ventricles in response to ventricular pressure and volume overload. Circulating levels of BNP are typically a fraction of ANP levels, but, in heart failure, the elevation of BNP is significantly higher, making it a better marker for both acute and chronic heart failure.

The timing of blood samples, particularly in the case of BNP, is an important limitation of this study. Because subjects had likely been awake for at least an hour prior to phlebotomy, the data do not exclude the possibility of nocturnal left ventricular strain in OSAH. However, the data are sufficient to conclude that, in this cohort, the nocturnal physiologic effects of OSAH do not translate into awake left ventricular dysfunction as manifested by natriuretic peptide levels. Moreover, these data are consistent with those of Moller et al., who measured natriuretic peptides at 8 am, as well as with those of Svatkova et al., who measured BNP levels at the start of and during the sleep period. Although Moller et al obtained negative results with morning awake natriuretic peptide samples, possibly having the same limitation as our study, the apparent association of OSAH with natriuretic peptide levels measured at 10 pm prior to the sleep period in the Kita et al study suggests that the timing of natriuretic peptide sampling does not explain the difference between that study and ours.

The lack of increase in plasma natriuretic peptide levels with increasing severity of OSAH in a community-based sample indicates that OSAH in this setting is not associated with persistent daytime left ventricular dysfunction, as reflected in morning

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plasma natriuretic peptide levels. Caution should be exercised in extrapolating from clinic-based studies that suggest a positive association between AHI and natriuretic peptide levels to the large number of undiagnosed cases of OSAH in the general population.

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REFERENCES


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