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Athanasios G. Kaditis, MD; Emmanouel I. Alexopoulos, MD; Fotini Hatzi, MSc; Eleni Kostadima, MD; Maria Kiaffas, MD; Epameinondas Zakynthinos, MD; and Konstantinos Gourgoulianis, MD

Study objectives: **Obstructive sleep-disordered breathing is accompanied by episodic increases in left ventricle afterload due to large negative swings in intrathoracic pressure and repetitive surges in arterial pressure. Brain natriuretic peptide (BNP) is released by ventricular myocytes in response to pressure and volume overload. It was hypothesized that in children with snoring, overnight change in BNP levels is correlated with severity of disturbance in respiration.**

Design: **Evening and morning plasma levels of BNP were measured in children with snoring referred for polysomnography.**

Setting: **A sleep disorders laboratory in a university hospital.**

Participants: **Twenty-two children with apnea-hypopnea index (AHI) ≥ 5/h (mean ± SD age, 6.4 ± 2.5 years), 60 children with AHI < 5/h (mean age, 7 ± 2.9 years), and 27 control subjects without snoring (mean age, 7.8 ± 3.7 years) were recruited.**

Measurements and results: **Overnight change in BNP (log-transformed ratio of morning-to-evening levels) was larger in children with AHI ≥ 5/h, compared to those with AHI < 5/h or to control subjects (0.1 ± 0.19 vs 0.01 ± 0.14 vs − 0.06 ± 0.18; p < 0.05). Children with AHI ≥ 5/h had an odds ratio of 4.33 (95% confidence interval, 1.34 to 14) for change in peptide levels > 0.15 relatively to subjects with AHI < 5/h. AHI and oxygen saturation of hemoglobin nadir were significant predictors of overnight change in peptide levels.**

Conclusions: **In children with snoring, overnight increase in BNP levels is correlated with severity of disturbance in respiration during sleep, which may indicate presence of nocturnal cardiac strain.** ***(CHEST 2006; 130:1377–1384)***

Key words: atherosclerosis; obstructive sleep apnea; snoring; ventricular hypertrophy

Abbreviations: AHI = apnea-hypopnea index; BNP = brain natriuretic peptide; Sa_{O_2} = oxygen saturation of hemoglobin

Obstructive sleep-disordered breathing is due to intermittent upper airway obstruction and is characterized by increased work of breathing, more negative than usual intrathoracic pressure during inspiration, microarousals and, in many subjects, blood gas exchange abnormalities.[1] The previous immediate responses to intermittent upper airway obstruction during sleep are associated with a second series of more sustained changes that potentially predispose adults and children to future cardiovas-

*From the Departments of Pediatrics (Dr. Kaditis, Dr. Alexopoulos, and Mrs. Hatzi) and Critical Care Medicine (Drs. Kostadima and Zakynthinos) and the Sleep Disorders Laboratory (Dr. Gourgoulianis), University of Thessaly School of Medicine and Larissa University Hospital, Larissa; and the Department of Pediatric Cardiology (Dr. Kiaffas), Onassis Cardiac Surgery Center, Athens, Greece.

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Correspondence to: Athanasios Kaditis, MD, Department of Pediatrics, Larissa University Hospital, PO Box 1425, Larissa 41110, Greece; e-mail: KADITIA@hotmail.com

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cular morbidity. These alterations include but are not limited to endothelial dysfunction and decreased arterial distensibility[2,3]; inflammation and metabolic disturbances[4–8]; hypertension[9–11]; and changes in cardiac structure and function.[2,12–15] Hence, it is not surprising that obstructive sleep apnea in adults has been correlated with coronary artery disease, congestive heart failure, and stroke.[16]

Furthermore, obstructive sleep-disordered breathing in adults has been related to acute detrimental effects on the cardiovascular system, such as repetitive nocturnal oscillations in arterial BP,[17] that may also contribute to increased long-term cardiovascular morbidity. At the termination of an obstructive event, systemic BP rises, whereas cardiac stroke volume decreases probably because of increased ventricular afterload.[18] This response of the cardiovascular system to upper airway obstruction has been attributed to peripheral vasoconstriction resulting from sympathetic nervous system activation secondary to hypoxemia and microarousals.[19,20]

Several reports in children with obstructive sleep apnea-hypopnea have provided evidence consistent with long-term effects of increased load (strain) of the cardiac ventricles during apneic events. Severe obstructive sleep apnea-hypopnea may be accompanied by cor pulmonale,[21,22] and decreased right ventricular ejection fraction.[12,13] Reports[14,15] suggest that higher apnea-hypopnea index (AHI) is correlated with increased left cardiac ventricle mass index and decreased diastolic function.

Brain natriuretic peptide (BNP) is a neurohormone released by the cardiac ventricles in response to volume and pressure overload as it occurs in adult subjects with congestive heart failure or acute myocardial infarction.[23–25] In one study,[26] overnight increase of plasma BNP levels was documented in adults with obstructive sleep apnea but not in control subjects, most likely secondary to increased cardiac load related to intermittent upper airway obstruction during sleep. The main hypothesis of the current investigation has been that in children with habitual snoring, the higher the severity of obstructive sleep-disordered breathing, the larger the overnight change in plasma concentration of BNP. If this hypothesis is valid, the overnight increase in BNP levels in children with obstructive sleep apnea may indicate presence of cardiac ventricular strain.

Materials and Methods

Recruitment of Subjects and Clinical Evaluation

The study protocol was approved by the University of Thessaly Ethics Committee. Informed consent was obtained from parents of participants and the child's assent from subjects > 6 years old. Consecutive children with snoring (> 3 nights/wk) for the last 6 months who were referred to the sleep disorders laboratory were eligible for participation. Children without snoring were recruited as control subjects. Exclusion criteria for participation of children with snoring or of control subjects without snoring were symptoms of respiratory tract infection, and history of cardiovascular, renal, neuromuscular, or genetic disorders. Eighteen participants of this investigation have also been included in a previous study[27] by the current authors.

Parents were interviewed regarding symptoms of sleep-disordered breathing and a history of adenoidectomy or tonsillectomy. Subjects underwent a physical examination, and body mass index z-score was calculated.[28] Morning BP was measured three times, and the average value was used in statistical analysis.[29] To control for the effect of age, gender, and height on BP, an index was calculated: (average measured value − 95th percentile value) × 100/95th percentile value.[29,30]

Polysomnography

All participants, except for control subjects without snoring, underwent overnight polysomnography in the Sleep Disorders Laboratory of Larissa University Hospital under the supervision of trained personnel. The Alice 4 computerized system (Healthdyne; Marietta, GA) was used to record the following parameters: EEG (C3/A2, C4/A1, O1/A2); right and left oculogram; submental and tibial electromyogram; body position; ECG; thoracic and abdominal wall motion (piezoelectric transducers); oronasal airflow (three-pronged thermistor); and oxygen saturation of hemoglobin (Sao_2). End-tidal carbon dioxide was not monitored during the sleep study. Bedtime was determined by each child's routine, and polysomnography was terminated on final awakening.

Arousals and sleep stages were assessed using standard criteria.[31,32] Total sleep time was determined based on both EEG and the laboratory technician's notes. Obstructive apnea was defined as the presence of chest/abdominal wall motion in the absence of airflow for at least two breaths in duration.[10,33] Hypopnea was defined as follows: (1) a reduction in the airflow signal amplitude of at least 50% compared to baseline, (2) presence of chest/abdominal wall motion, and (3) association with oxygen desaturation of hemoglobin ≥ 4% or with an arousal.[30] The AHI is the number of obstructive and mixed apneas (apneas with both central and obstructive components) and hypopneas per hour of sleep. The frequency of arousals terminating apneas or hypopneas determined the respiratory arousal index. The number of episodes per hour of oxygen desaturation of hemoglobin ≥ 4% (oxygen desaturation of hemoglobin index), Sao_2 nadir, and percentage of sleep time with $Sao_2 < 95\%$ were also calculated.

BNP Measurement

Venous blood collection was performed prior to bedtime and between 8:00 AM and 10:00 AM. BNP concentration was measured in ethylenediamine tetra-acetic acid-anticoagulated blood using the Triage Meter Plus device (Biosite Diagnostics; San Diego, CA) immediately after blood sample collection.[34] Interassay coefficients of variation of this fluorescent immunoassay are as follows: 10%, 12.4%, and 14.8% for BNP concentrations of 28.8 pg/mL, 584 pg/mL, and 1,180 pg/mL, respectively. Lowest detection limit of the method is 5 pg/mL. Measurements lower than the lowest detection limit were considered equal to 5 pg/mL.

Data Analysis

In order to evaluate the risk for increased overnight change of BNP levels in children with moderate-to-severe obstructive

sleep-disordered breathing compared to subjects with mild disturbance in respiration during sleep, three study groups were formed: (1) children with snoring and AHI ≥ 5/h; (2) children with snoring and AHI < 5/h; and (3) control subjects without snoring. The AHI cutoff value of 5/h was selected because in many pediatric hospitals this value is used as an indication for adenotonsillectomy in children with snoring.[35]

BNP values were log-transformed to obtain a normal distribution. Study groups were compared regarding evening and morning BNP plasma levels, overnight change in BNP (log-transformed morning-to-evening BNP ratio), and variables that may affect the previous values. χ^2 test was applied for comparisons regarding categorical characteristics, and one-way analysis of variance was used for continuous characteristics. One-way analysis of variance was followed by *post hoc* tests for pair comparisons between study groups. The two groups of children with snoring were compared regarding polysomnography indices by Student *t* test.

Odds ratio for overnight change in BNP > 0.15 in children with AHI > 5/h relatively to participants with AHI < 5/h was calculated. A log-transformed BNP ratio > 0 reflects a higher morning level than evening level. Since this was the first study exploring overnight change in BNP in children with snoring, several cutoff values for log-transformed BNP ratio were explored for estimating the odds ratio. The 0.15 value was selected because it graphically best separated participants with higher overnight change in BNP plasma levels from those with a lower BNP change.

Pearson correlation was performed to identify associations between overnight change in BNP levels and the following: (1) body mass index z-score, (2) morning systolic BP index, (3) morning diastolic BP index, and (4) polysomnography indices. Values of polysomnography indices (AHI, respiratory arousal index, oxygen desaturation of hemoglobin index, Sao_2 nadir, and percentage of sleep time with Sao_2 < 95%) were log-transformed so that they approached a normal distribution. Pearson correlation was repeated for the log-transformed values.

Multiple linear regression was applied to detect independent predictors of overnight change in BNP levels (SPSS version 10.0; SPSS, Chicago, IL). Age, gender, body mass index z-score, morning systolic and diastolic BP index, and AHI or Sao_2 nadir were entered as independent variables in the regression analysis model. Systolic and diastolic BPs were examined as possible predictors of overnight change in plasma BNP, as it was hypothesized that they reflect pressure load on the myocardium of the left ventricle. Multivariable analysis was repeated using log-transformed AHI or log-transformed Sao_2 nadir as independent variables.

Results

Subject Characteristics

A total of 109 children were studied. The age range of participants was 2.3 to 14 years. Subject characteristics and polysomnography findings are summarized in Table 1. There were no differences regarding age, female-to-male ratio, body mass index z-score, and morning systolic or diastolic BP index among the three study groups.

BNP Values

Mean ± SD evening plasma BNP values in snorers with AHI ≥ 5/h, snorers with AHI < 5/h, and control subjects without snoring were as follows: 8.8 ± 7.7 pg/mL (range, 5 to 40.2 pg/mL), 7.9 ± 4.5 pg/mL (range, 5 to 27.2 pg/mL), and 9.7 ± 5.2 pg/mL (range, 5 to 23.6 pg/mL), respectively. Mean morning BNP values in snorers with AHI ≥ 5/h, snorers with AHI < 5/h, and control subjects without snoring were as follows: 11 ± 7.6 pg/mL (range, 5 to 32.2 pg/mL), 8.2 ± 5.2 pg/mL (range, 5 to 35.2 pg/mL), and 8.7 ± 5.6 pg/mL (range, 5 to 25.4 pg/mL), respectively. Mean evening-to-morning BNP level ratios in the previous groups were as

Table 1—*Summary Statistics and Significance of Comparisons Among Study Groups Regarding BNP Plasma Levels and Variables That May Affect These Levels

Variables	Snoring and AHI ≥ 5/h (n = 22)	Snoring and AHI < 5/h (n = 60)	Control Subjects Without Snoring (n = 27)
Age, yr	6.4 ± 2.5	7 ± 2.9	7.8 ± 3.7
Female gender, No. (%)	8 (36.4)	22 (36.7)	12 (44.4)
Body mass index z-score	0.59 ± 1.22	0.64 ± 1.23	0.86 ± 1.01
Morning systolic BP index, %	− 14 ± 11	− 17.1 ± 9.9	− 14.8 ± 9.7
Morning diastolic BP index, %	− 8.8 ± 11.6	− 12.9 ± 14.3	− 11.9 ± 13.2
AHI, /h†	12.2 ± 6.2	2 ± 1.1	
Respiratory arousal index, /h†	3.3 ± 1.8	1.1 ± 2.1	
Oxygen desaturation of hemoglobin (≥ 4%) index, /h†	11.3 ± 6.6	1.5 ± 1	
Sao_2 nadir, %†	82.6 ± 6.5	90.3 ± 3.1	
Percentage of sleep time with Sao_2 < 95%†	15.6 ± 23.6	0.88 ± 0.98	
Log evening BNP level	0.87 ± 0.23	0.85 ± 0.18	0.93 ± 0.23
Log morning BNP level	0.97 ± 0.24	0.87 ± 0.19	0.87 ± 0.23
Log morning-to-evening BNP ratio‡	0.10 ± 0.19	0.01 ± 0.14	− 0.06 ± 0.18

*Continuous variables are expressed as mean ± SD.

†$p < 0.05$ for comparisons of snorers with AHI ≥ 5 vs snorers with AHI < 5.

‡$p < 0.05$ for comparisons of snorers with AHI ≥ 5 vs snorers with AHI < 5 and vs control subjects.

follows: 1.4 ± 0.63 (range, 0.55 to 2.84), 1.08 ± 0.3 (range, 0.32 to 1.66), and 0.93 ± 0.3 (range, 0.27 to 1.52).

All three groups had similar log-transformed evening BNP values (Table 1). There was a trend for higher log-transformed morning BNP values in children with AHI ≥ 5/h compared to the other groups that did not achieve statistical significance ($p = 0.14$) [Table 1]. Snorers with AHI ≥ 5/h had higher overnight change in BNP levels than snorers with AHI < 5/h, or control subjects without snoring ($p < 0.05$) [Table 1, Fig 1]. The odds ratio for an overnight change in BNP > 0.15 in children with AHI ≥ 5/h in relation to children with AHI < 5/h was 4.33 (95% confidence interval, 1.34 to 14).

Predictors of Overnight BNP Change

AHI was not correlated with BMI z-score ($r = -0.08$; $p > 0.05$). Significant univariate correlations of overnight change in BNP with BMI z-score, AHI (Fig 2), oxygen desaturation of hemoglobin index, and SaO_2 nadir (Fig 3) were identified (Table 2). Results of univariate correlations were similar when log-transformed values of the polysomnography indices were used (Table 2).

Multivariable analysis revealed that AHI, SaO_2 nadir, and female gender were significant predictors of the overnight change in BNP levels (Table 3). When the multivariable analysis was repeated using log-transformed values of AHI and SaO_2 nadir, independent predictors of overnight change in BNP levels were the same. Adjusted r^2 values were also similar ($r^2 = 0.16$ and $p < 0.01$ for the log AHI model; $r^2 = 0.17$ and $p < 0.01$ for the log SaO_2 nadir model).

In the regression analysis model including AHI (but not log AHI) and systolic and diastolic BP indices as independent variables, systolic BP index was a significant predictor of the overnight change in BNP, although there was not a significant correlation between the two variables in univariate analysis. This

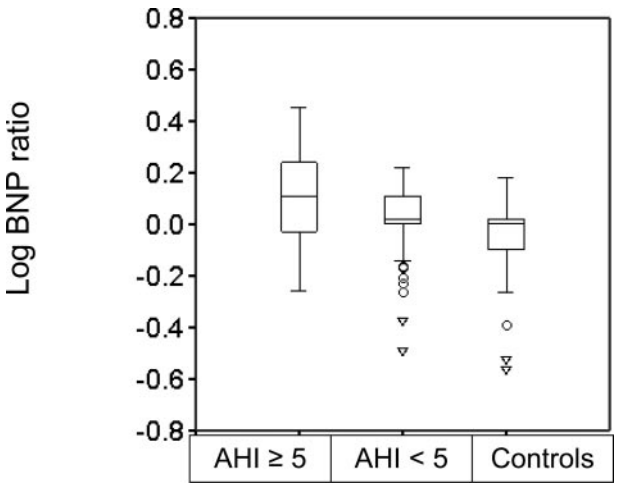

FIGURE 1. Box plots of overnight change in BNP plasma levels (log-transformed morning-to-evening BNP ratio) in children with habitual snoring and AHI ≥ 5/h (n = 22), children with habitual snoring and AHI < 5/h (n = 60), and control subjects without snoring (n = 27). Overnight change in BNP is higher in snorers with AHI ≥ 5/h compared to children with AHI < 5/h or to control subjects without snoring ($p < 0.05$). Horizontal bars represent median, whiskers represent highest and lowest values, circles are outliers, and triangles are extreme values.

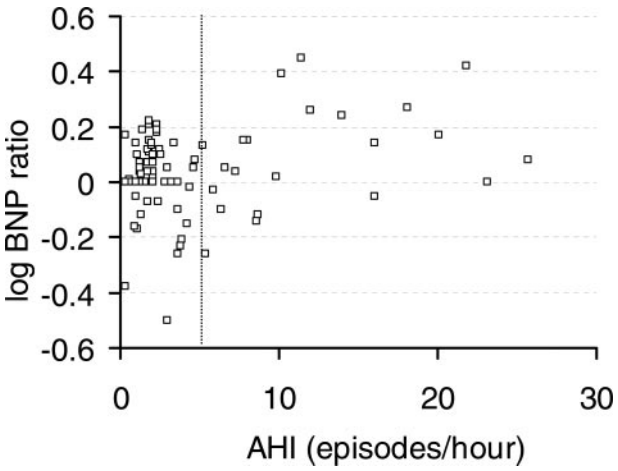

FIGURE 2. Scatter plot of overnight change in BNP plasma levels (log-transformed morning-to-evening BNP ratio) plotted against AHI for 82 children with habitual snoring ($r = 0.3$; $p < 0.05$). The odds ratio for overnight change in BNP > 0.15 in children with AHI ≥ 5/h (values beyond vertical dotted line) in relation to children with AHI < 5/h was 4.33 (95% confidence interval, 1.34 to 14).

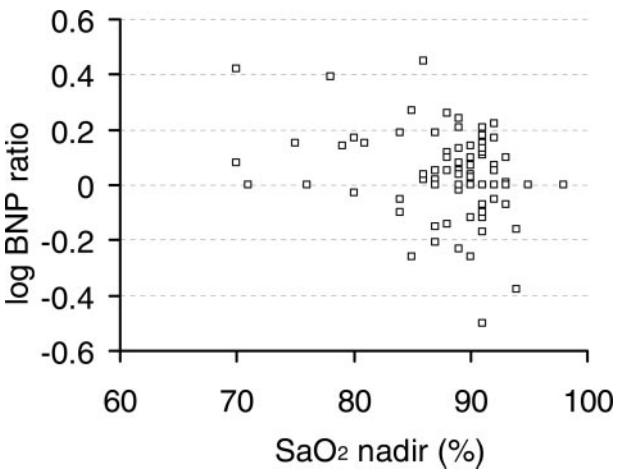

FIGURE 3. Scatter plot of overnight change in BNP levels (log-transformed morning-to-evening BNP ratio) plotted against SaO_2 nadir for 82 children with habitual snoring ($r = -0.29$; $p < 0.05$).

Table 2—*Pearson Correlation Coefficients Relating Overnight Change in BNP Plasma Levels (Log Morning-to-Evening BNP Ratio) With Body Mass Index Z-Score, BP, and Polysomnography Indices

Variables	*r* Value
Body mass index z-score	− 0.23†
Systolic BP index	− 0.1
Diastolic BP index	0.03
AHI	0.3† (0.26†)
Respiratory arousal index	0.19 (0.22)
Oxygen desaturation of hemoglobin (≥ 4%) index	0.29† (0.25†)
SaO_2 nadir	− 0.29† (−0.29†)
Percentage of sleep time with $SaO_2 < 95\%$	0.16 (0.22)

*Correlation coefficients for log-transformed polysomnography indices are shown in parentheses.
†$p < 0.05$.

was due to the significant interaction between systolic and diastolic BP indices ($r = 0.54$; $p < 0.0001$).

Discussion

An overnight increase in BNP plasma levels that is larger in children with habitual snoring and AHI ≥ 5/h compared to subjects with AHI < 5/h or to control subjects without snoring has been demonstrated in the current study. This change is positively correlated with indices of severity of sleep-disordered breathing. Children with AHI ≥ 5/h have a four-times-higher risk for nocturnal increase in BNP (log-transformed morning-to-evening BNP ratio) > 0.15 compared to subjects with AHI < 5/h. We speculate that overnight change in BNP concentration is the result of raised cardiac ventricular load associated with intermittent upper airway obstruction during sleep.

Log-transformed morning-to-evening BNP ratio was associated not only with AHI but also with variables describing oxygenation during sleep (*eg*, oxygen desaturation of hemoglobin index). This is because the definition of AHI incorporates episodes of oxygen desaturation of hemoglobin and thus AHI correlates with polysomnography indices describing oxygenation. It is surprising that there was a negative univariate correlation between overnight change in BNP and BMI z-score, as one would expect that more obese children would have more severe sleep-disordered breathing. However, in participants of the current report AHI was not associated with BMI z-score.

BNP has been named so because it has been initially detected in porcine brain,[36] although its concentration is much higher in the heart.[37] It is produced mainly by myocytes of the cardiac ventricles as a prohormone and is released in the circulation in response to increased pressure and volume cardiac load (ventricular strain). Acute overload of the cardiac ventricles leads to induction of BNP gene expression and secretion of the peptide in the bloodstream.[23] Increased levels of BNP have been reported in children with heart failure of various causes, congenital cardiac anomalies causing left-to-right shunt, or pulmonary hypertension.[38] Vasodilatation and natriuresis are some of the BNP biological actions that tend to reduce cardiac ventricular overload.[39]

Other conditions except for direct increased load to ventricular myocardium that may affect release of BNP include traumatic brain injury,[40] hyperthyroidism,[41] cirrhosis,[42] biliary atresia associated with cirrhosis,[43] liver transplantation,[43] and chronic renal failure.[44] No participants in the present investigation had any of the previous disorders, and for this reason we suggest that the overnight increase in BNP levels in children with snoring was related to pressure and volume load to ventricular myocardium associated with sleep-disordered breathing.

A number of studies and case reports[12–15,22] in children with obstructive sleep-disordered breathing have provided indirect evidence for the presence of chronic strain of right and left cardiac ventricles associated with sleep apnea. Children with severe obstructive sleep apnea-hypopnea can present with

Table 3—*Multiple Linear Regression Analysis Models Assessing the Independent Effect of Different Variables on Overnight Change in BNP Plasma Levels (Log Morning-to-Evening BNP Ratio)*

	Dependent Variable Log Morning-to-Evening BNP Ratio	
Independent Variables	β (Standardized Coefficient)	p Value
Model 1 (adjusted $r^2 = 0.18$; $p < 0.01$)		
AHI	0.347	< 0.01
Age	0.253	0.06
Gender (1 = male; 2 = female)	0.314	< 0.01
Body mass index z-score	− 0.19	0.09
Systolic BP index	− 0.332	0.03
Diastolic BP index	0.259	0.09
Model 2 (adjusted $r^2 = 0.17$; $p < 0.01$)		
SaO_2 nadir	− 0.317	< 0.01
Age	0.211	0.12
Gender (1 = male; 2 = female)	0.313	< 0.01
Body mass index z-score	− 0.206	0.07
Systolic BP index	− 0.293	0.06
Diastolic BP index	0.233	0.13

cor pulmonale and pulmonary hypertension,[22] while decreased right ventricle ejection fraction has been identified by echocardiography and radionuclide ventriculography in pediatric subjects with adenotonsillar hypertrophy and sleep apnea.[12,13] Both right and left cardiac ventricle ejection fraction improve after adenotonsillectomy.[12] Amin and colleagues[14] reported that in children with snoring the higher the AHI, the higher the risk for increased right cardiac ventricle end-diastolic dimension and increased left ventricle mass index. The same investigators[15] found a negative correlation between severity of obstructive sleep apnea-hypopnea and left cardiac ventricle diastolic function.

Mechanisms responsible for the presence of ventricular strain and abnormalities in myocardial structure and function in children with intermittent upper airway obstruction during sleep have not been fully clarified.[12–15] Evidence from studies[45,46] in adults and experimental animals indicate that at the termination of apnea, stroke volume of both the right and left cardiac ventricles decreases. Reduction in stroke volume may be due to increased ventricular afterload secondary to repetitive increases in pulmonary artery pressure and systemic BP (peripheral vasoconstriction) at the end of an obstructive event.[19,47]

In addition, upper airway obstruction is accompanied by exaggerated negative intrathoracic pressure swings, increased systemic venous return, and preload to the right ventricle that displaces the intraventricular septum toward the left ventricle free wall.[12] This displacement impairs left cardiac ventricle filling and along with increased afterload contributes to the reduction in stroke volume.[18,46] Increased left cardiac ventricle afterload is probably due not only to peripheral vasoconstriction but also to large negative swings in intrathoracic pressure.[47,48]

Chronic nocturnal increase in ventricular afterload may lead to increased left cardiac ventricle mass, an important risk factor for future cardiovascular disease such as congestive heart failure.[49] Therefore, changes in cardiac structure[14] and function,[12,13,15] along with: (1) reduced arterial distensibility[3]; (2) increased BP variability, decreased nocturnal BP dipping, or even sustained BP elevation[10,11,30]; and (3) chronic inflammation and insulin resistance,[5,6,8] may predispose children with sleep-disordered breathing to increased risk for cardiovascular morbidity in adulthood.

In the above described context, the usefulness of measuring plasma BNP levels in children with sleep-disordered breathing remains to be elucidated. Further studies are necessary to investigate the possible correlation of cardiac ventricle anatomy and function with overnight change in BNP plasma concentration as well as the potential effect of adenotonsillectomy on BNP levels. If such correlations exist, then BNP could be possibly used in clinical practice as an index of increased ventricular load secondary to intermittent upper airway obstruction during sleep.

It should be noted, however, that correlation of the overnight change in BNP levels with AHI is rather weak and there is overlap between low-AHI and high-AHI subjects regarding this change. The previous observation indicates that intermittent upper airway obstruction during sleep is only one of the factors affecting BNP plasma levels and that other parameters possibly play an important role in BNP release from ventricular myocytes overnight.

Two important arguments against the speculation that overnight increase in BNP plasma concentration reflects acute strain of the cardiac ventricles associated with nocturnal intermittent upper airway obstruction need to be discussed. First, the magnitude of mean overnight BNP change in children with sleep apnea is small (approximately 25%) compared to the dramatic rise of BNP levels in children and adults with congestive heart failure.[24,34,50] Nevertheless, clinical presentation and myocardial strain in subjects with cardiac failure are far more severe than the subtle abnormalities identified by echocardiography in otherwise healthy children with obstructive sleep apnea.

Second, studies[26,51] assessing the correlation of BNP levels with severity of obstructive sleep apnea in adults have provided contradictory results. Kita and colleagues[26] recorded increasing BNP levels in the second half of sleep time (2:00 to 6:00 AM) that was correlated with average apnea duration. Svatikova and colleagues[51] did not identify a change in BNP concentration between 2 AM and 6 AM, but during this sleep period participants were undergoing a therapeutic continuous positive airway pressure trial. Since BNP should be first synthesized and then released by ventricular myocytes in response to pressure and volume overload, it is conceivable that BNP levels do not increase in adults with sleep apnea prior to midnight. In a third investigation,[52] adult subjects with obstructive sleep apnea and controls free of sleep disturbances were recruited. BNP levels were measured only in the morning, and no difference was identified between study groups. Treatment with continuous positive airway pressure for 12 to 17 months did not affect morning BNP plasma concentrations.

When male subjects with a mean age of 68.6 ± 10 years and congestive heart failure were studied,[53] it was demonstrated that the lower the left ventricular ejection fraction, the higher the prevalence of sleep-disordered breathing and the concentration of BNP. This finding was in contrast to results of another investigation[54] that recruited male and female sub-

jects with a mean age of 60.1 ± 9.8 years and congestive heart failure. Concentrations of the amino-terminal fragment of pro-BNP were similar in participants with and without sleep-disordered breathing. Amino-terminal fragment is produced when BNP is released from pro-BNP. Finally, when patients with stable heart failure and disturbed breathing during sleep used a mandibular advancement device, they had not only an improvement in sleep apnea but a reduction in BNP levels as well.[55]

In conclusion, overnight rise of BNP blood concentration in children with obstructive sleep-disordered breathing is positively correlated with severity of the disturbance in respiration during sleep and may indicate nocturnal cardiac strain. The potential association of reported abnormalities in anatomy and function of the cardiac ventricles with the overnight BNP increase in children with obstructive sleep apnea needs to be assessed.

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Athanasios G. Kaditis, Emmanouel I. Alexopoulos, Fotini Hatzi, Eleni Kostadima, Maria Kiaffas, Epameinondas Zakynthinos and Konstantinos Gourgoulianis

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