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Hypoxia, Not the Frequency of Sleep Apnea, Induces Acute Hemodynamic Stress in Patients With Chronic Heart Failure

Joshua D. Gottlieb, AM,* Alan R. Schwartz, MD,† Joanne Marshall,‡ Pamela Ouyang, MBBS,†
Linda Kern,† Veena Shetty, MPH,§ Maria Trois,† Naresh M. Punjabi, MD, PHD,†
Cynthia Brown, MD,‖ Samer S. Najjar, MD,¶ Stephen S. Gottlieb, MD‡

Cambridge, Massachusetts; Baltimore, Maryland; and Charlottesville, Virginia

Objectives	This study was conducted to evaluate whether brain (B-type) natriuretic peptide (BNP) changes during sleep are associated with the frequency and severity of apneic/hypopneic episodes, intermittent arousals, and hypoxia.
Background	Sleep apnea is strongly associated with heart failure (HF) and could conceivably worsen HF through increased sympathetic activity, hemodynamic stress, hypoxemia, and oxidative stress. If apneic activity does cause acute stress in HF, it should increase BNP.
Methods	Sixty-four HF patients with New York Heart Association functional class II and III HF and ejection fraction <40% underwent a baseline sleep study. Five patients with no sleep apnea and 12 with severe sleep apnea underwent repeat sleep studies, during which blood was collected every 20 min for the measurement of BNP. Patients with severe sleep apnea also underwent a third sleep study with frequent BNP measurements while they were administered oxygen. This provided 643 observations with which to relate apnea to BNP. The association of log BNP with each of 6 markers of apnea severity was evaluated with repeated measures regression models.
Results	There was no relationship between BNP and the number of apneic/hypopneic episodes or the number of arousals. However, the burden of hypoxemia (the time spent with oxygen saturation <90%) significantly predicted BNP concentrations; each 10% increase in duration of hypoxemia increased BNP by 9.6% (95% confidence interval: 1.5% to 17.7%, p = 0.02).
Conclusions	Hypoxemia appears to be an important factor that underlies the impact of sleep abnormalities on hemodynamic stress in patients with HF. Prevention of hypoxia might be especially important for these patients. (J Am Coll Cardiol 2009;54:1706–12) © 2009 by the American College of Cardiology Foundation

Sleep apnea has been strongly associated with heart failure (HF) in various cross-sectional studies, with a reported prevalence as high as 40% in HF patients (1,2). Although

the extent to which sleep apnea reflects HF severity or causes worsening HF is controversial, there are suggestions that sleep apnea can be harmful. Heart failure patients with sleep apnea have a worse prognosis than do patients without sleep apnea (3,4), and treating sleep apnea can improve hemodynamics, alleviate cardiovascular stress, and potentially prolong survival in HF patients (5,6).

The hallmark of sleep apnea is recurrent episodes of hypoxemia and arousals throughout the night. These arousals are accompanied by bursts of sympathetic stimulation that elicit peripheral vasoconstriction and an increase in heart rate and blood pressure (7). Furthermore, the mechanical stresses in obstructive sleep apnea can lead to an increase in left ventricular afterload with further compromise of cardiac output (8). Hypoxia itself can have direct detrimen-

tal cardiac effects (9). Thus, increased sympathetic activity, hemodynamic stress, and hypoxia could all potentially cause exacerbation of HF.

Brain (B-type) natriuretic peptide (BNP) is a polypeptide with a short half-life ($\approx$20 min) that is secreted by the ventricles in response to cardiomyocyte stretching, and thus is a good marker of hemodynamic stress. If apneic episodes cause acute stress in patients with HF, then BNP levels would be expected to rise and fall contemporaneously. We hypothesized that in patients with HF, the changes in the concentrations of BNP during the night are associated with the frequency of apneic/hypopneic episodes and arousals, as well as the severity of hypoxemia. To address these hypotheses, we designed a study that could evaluate the immediate effects of sleep disturbances on BNP by measuring BNP levels every 20 min during sleep and characterizing the sleep and breathing patterns during these same 20-min blocks.

Methods

Study Design

Patient selection. Subjects were recruited from the patient populations at Johns Hopkins Bayview Medical Center and the University of Maryland. All patients had stable symptomatic HF and a left ventricular ejection fraction ≤40%. They were euvolemic and on a stable HF medication regimen for at least 1 month. Patients were excluded if they had unstable angina, myocardial infarction, or hospitalization within the previous 2 months.

Study protocol. Patients underwent 3 nights of study. On night 1 (baseline test), patients were acclimatized to the sleep laboratory and underwent a standard sleep study to characterize their sleep and breathing patterns. Baseline recordings were analyzed to categorize patients into 1 of 3 groups: no or mild sleep apnea present, overall apnea-hypopnea index (AHI) ≤5; sleep apnea of intermediate severity, AHI 6 to 39.9; or severe sleep apnea, AHI ≥40.

Patients with no to mild sleep apnea and patients with severe sleep apnea were selected for further study to examine the effects of apnea on BNP. They subsequently underwent a second sleep study, now with blood sampling every 20 min. (We refer to each sampling interval as an "epoch.") Patients with intermediate sleep apnea were not further studied because we desired to maximize our sensitivity to detect significant effects of sleep apnea on BNP. Those patients with intermediate sleep apnea were similar to the patients who underwent blood sampling (Table 1).

After at least 2 weeks, patients with severe sleep apnea underwent a third sleep study with frequent blood sampling and also with administration of supplemental oxygen (intervention night). The data from the 2 nights with frequent blood sampling obtained from subjects with severe sleep apnea together with the 1 night of blood sampling obtained from subjects with no or mild sleep apnea on the baseline test form the basis of the present study. (Note that some of the subjects without sleep apnea on baseline testing had

mild or moderate sleep apnea on repeat testing; the group with AHI ≤5 on baseline testing is referred to as mild sleep apnea throughout this paper).

By comparing the BNP obtained during the normal sleep epochs with the BNP obtained during epochs with sleep abnormalities, the multiple time points provide the power to look at the immediate effects of apneic episodes, arousals, and hypoxia on BNP. We evaluated 12 HF patients with severe sleep apnea, both with and without supplemental oxygen, and 5 HF patients with mild to moderate sleep apnea on the baseline test. This provided 643 time-series measurements of BNP levels and apnea counts.

Sleep recording methods. Standardized recording methods were utilized as previously described (10) and included continuous monitoring of left and right electro-oculogram, submental electromyogram, C_3 to A_2 and C_3 to O_1 electroencephalogram, anterior tibialis electromyogram, oronasal airflow as assessed by both a pressure-sensitive nasal cannula and a thermistor, pulse oximetry, and thoracic and abdominal movements with piezo-electric gauges, and a modified V_5 electrocardiography lead for cardiac rhythm monitoring. Patients were admitted to the unit at 5:00 PM for the sleep study. Thereafter, a standardized meal was provided for dinner at 6:00 PM. Sleep study recording sensors were applied, and a forearm intravenous catheter

Abbreviations and Acronyms
AHI = apnea-hypopnea index
BNP = brain (B-type) natriuretic peptide
CSA = central sleep apnea
HF = heart failure
OSA = obstructive sleep apnea
SaO₂ = oxygen saturation
t90 = percentage of time spent during each epoch at oxygen saturation levels <90%

Table 1	Baseline Characteristics of Subjects Found to Have Moderate Sleep Apnea, Mild (or No) Sleep Apnea, and Severe Sleep Apnea on Baseline Study*		
	Moderate Sleep Apnea (n = 47)	Mild Sleep Apnea (n = 5)	Severe Sleep Apnea (n = 12)
Age, yrs	59 ± 12	56 ± 12	61 ± 13
Sex, male	36 (76%)	3 (60%)	11 (92%)
Race, African-American	11 (23%)	1 (20%)	4 (33%)
Ejection fraction, %	20 ± 7	25 ± 6	19 ± 4†
Cardiomyopathy, ischemic	26 (55%)	2 (40%)	6 (50%)
Heart rate, min⁻¹	68 ± 9	76 ± 12	64 ± 11†
Body mass index, kg/m²	32 ± 7	32 ± 7	34 ± 8
Prescribed medications			
Beta-blockers	63 (97%)	5 (100%)	12 (100%)
ACE inhibitors or ARB	45 (95%)	5 (100%)	12 (100%)
Loop diuretic	41 (87%)	4 (80%)	10 (83%)
BNP prior to sleep, pg/ml		85 ± 90	243 ± 469

*Patients with moderate sleep apnea did not have subsequent study days with blood sampling.
†p < 0.05 patients with severe sleep apnea compared with patients who had mild sleep apnea on baseline study.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = brain (B-type) natriuretic peptide.

was placed. The sleep study commenced at 10:00 PM (lights out) and ended at 6:00 AM the next morning.

Frequent venous sampling protocol. Venous blood was drawn every 20 min for BNP. An initial baseline sample was drawn at 10:00 PM at "lights out." The next sample was drawn at 10:40 PM and every 20 min thereafter until 6:00 AM. The values recorded during the initial 40-min epoch of all data that are recorded in the form of counts per epoch are deflated by 50% to make the frequencies comparable to those recorded during subsequent 20-min epochs.

Analytic Methods

Sleep study analysis. Standard methods for evaluating sleep structure and respiratory patterns were applied to all sleep study recordings and are detailed in the Online Appendix.

Assays. Samples were spun down and stored at −70°C. The BNP (pg/ml) was assayed by radioimmunoassay (fluorescence immunoassay, Biosite, Inc., San Diego, California).

Primary analysis. We used the data to look for an association between apnea episodes and BNP concentrations over the time the subjects were observed. With 17 subjects, 11 of whom were monitored for 2 nights, and 23 observations per patient per night (except for 1 patient who had 1 less observation), we have 643 observations with which to relate apnea to BNP. (Blood testing was not performed on 1 of the 12 treatment subjects during the intervention night, so no BNP data are available for this subject for that night.) For each observation, we can relate the BNP concentration to sleep-disordered breathing exposure over the preceding 20-min epoch. To account for differences between treatment and nontreatment nights, different nights on which the same subject was observed are treated as independent observations.

In the primary analyses, we modeled the contemporaneous effects of sleep-disordered breathing activity on BNP. Our major predictor variables consisted of measures of sleep-disordered breathing severity. These metrics included the number of disordered breathing episodes (total, central, and obstructive), the number of arousals, and the severity of oxyhemoglobin desaturation during each 20-min epoch. The severity of intermittent desaturation was reflected by the average difference in oxygen saturation (SaO_2) from the start to the end of each sleep-disordered breathing episode (average low SaO_2). The overall severity of hypoxemia was represented by the percentage of time spent during each 20-min epoch at SaO_2 levels <90% (t90).

The fundamental challenge in analyzing these relationships is that multiple factors might cause changes in both BNP and apnea characteristics. With repeated measurements of BNP and the independent variables throughout the night, however, we can detect a relationship while accounting separately for variations across individual subjects and variations over time. We use a variety of standard time-series regression techniques to accomplish this.

Supplementary analyses. Because BNP remains in the blood after release by the left ventricle (with a half-life of approximately 20 min), and also because apneas could theoretically have a cumulative effect on hemodynamic stress, we investigated the possibility that apneas during a previous epoch may affect the level of BNP measured subsequently. We did this by adding 5 lags of the independent variable in our regressions, as shown in the Appendix equation (2). This allows us to measure the effect of apneas during the most recent epoch as well as the 5 previous 20-min periods on the current level of BNP. We are, therefore, able to detect the effect of 2 h worth of apneas on BNP. Further details are in the Online Appendix.

We conducted an additional analysis to distinguish between the effects of hypoxia associated with central sleep apnea (CSA) and hypoxia associated with obstructive sleep apnea (OSA). We first separated the 643 epochs based on the prevalence of the different types of apneas. We eliminated the 78 epochs with no sleep apneas and separated the remaining 565 epochs into 2 categories: predominantly CSA epochs were those in which at least one-half of the apneas were central (192 epochs); the remainder were considered predominantly OSA epochs.

Any difference between the impact of CSA-associated hypoxia on BNP and the impact of OSA-associated hypoxia on BNP should show up when we distinguish the frequency of hypoxemia during predominantly CSA epochs from the frequency during predominantly OSA epochs. We therefore ran a multivariate regression of log BNP on 2 separate hypoxemia variables. The first variable is equal to the percent of time during each predominantly CSA epoch that was spent with SaO_2 <90%, and it is equal to zero for all predominantly OSA epochs. Similarly, the second variable is equal to the percent of time that was spent with SaO_2 <90% during predominantly OSA epochs. As in Table 3, we ran a fixed-effects regression with clustered standard errors.

After the primary and secondary analyses discussed above, we checked the robustness of our general pattern of negative results to various changes in the model specification. The description of these analyses and the results are in the Online Appendix.

Results

The characteristics of the patients studied are described in Table 1. The patients with severe sleep apnea had a lower ejection fraction and a slower heart rate compared with patients who had mild sleep apnea.

The sleep study results are shown in Table 2. By design, the patients with severe apnea had more severe apneic and hypoxic parameters than did patients who had mild sleep apnea in the baseline study. These parameters were alleviated by supplementation of oxygen (night 3) compared with the study without an intervention (night 2). As previously described, oxygen led to a modest reduction in AHI (11)

Table 2	**Sleep Study Results of Patients With Mild Sleep Apnea at Baseline (Mild Sleep Apnea) and Those With Severe Sleep Apnea Without (Night 2) and With (Night 3) Oxygen Supplementation**		
	Mild Sleep Apnea	**Severe Sleep Apnea Night 2**	**Severe Sleep Apnea Night 3 (With O₂)**
Total apnea-hypopnea index	16 ± 8	66 ± 31	48 ± 18*
Percent obstructive apneas	93 ± 8	57 ± 37	74 ± 34*
Percent central apneas	2.2 ± 1.8	18 ± 25	15 ± 27
Percent mixed apneas	4.3 ± 7.4	26 ± 22	11 ± 14*
Total arousal index, n/h	13 ± 8	47 ± 23	39 ± 21
t90, %	0.49 ± 0.60	15.2 ± 19.6	1.7 ± 3.6*
Baseline SaO₂	96.9 ± 1.4	96.0 ± 2.0	98.1 ± 0.8*
Average low SaO₂, %	93.6 ± 2.0	88.9 ± 4.4	94.7 ± 2.4*
Baseline log BNP	3.5 ± 2.1	3.6 ± 2.6	4.5 ± 1.3
Mean log BNP	3.9 ± 1.3	3.5 ± 2.5	4.5 ± 1.4

*$p < 0.05$ night 3 versus night 2. Note that patients in the mild sleep apnea group had mild or no sleep apnea on the baseline study, but may have had mild to moderate sleep apnea on the subsequent study. Mean log brain (B-type) natriuretic peptide (BNP) refers to the mean of all samples obtained through the night.

SaO₂ = oxygen saturation; t90 = percentage of epoch spent at oxygen saturation levels <90%.

and an increased proportion of obstructive, compared with central and mixed apnea (12).

Figure 1 illustrates the time course of mean BNP and hypoxemia in each 20-min period through the night for all patients. At each time point, the percentage of time for that epoch spent with SaO_2 <90% (t90) is shown (dashed line). The values in the graph are the means for all patients. Similarly, the mean BNP concentrations for all patients are shown. Overall, no progressive change in BNP is detected over time. However, the individual fluctuations of BNP at various time points appear to coincide with t90.

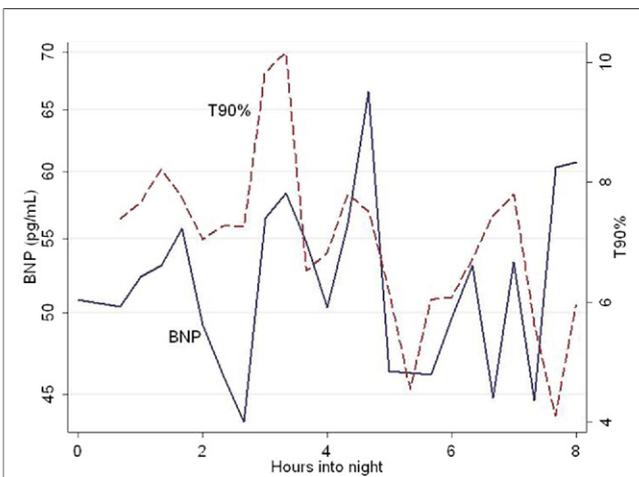Figure 2 demonstrates the time course of BNP (as described in the preceding text) and the number of sleep-
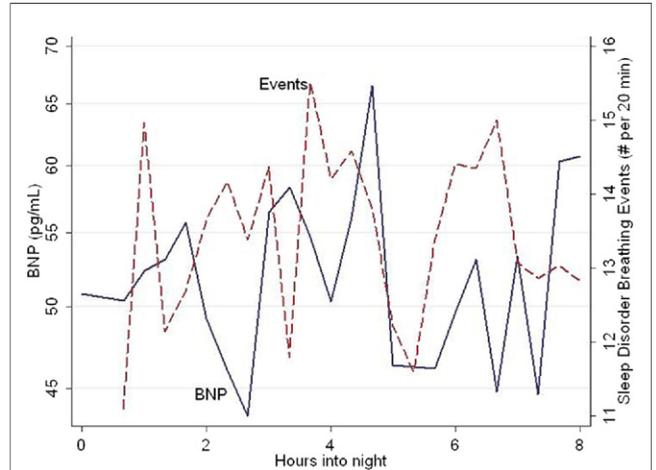
Figure 2   **Mean BNP and Frequency of Sleep-Disordered Breathing Episodes**

For each time point through the night, the mean brain (B-type) natriuretic peptide (BNP) of all patients **(solid line)** and the frequency of sleep-disordered breathing episodes **(dashed line)** are shown. Note that the BNP does not appear to fluctuate with the frequency of sleep-disordered breathing episodes.

disordered breathing episodes in each 20-min period through the night for all patients. There is no relationship between the number of sleep-disordered breathing episodes at each time point and the change in BNP.

The results of the primary regressions are presented in Table 3. Each row of the table shows the relationship between a different independent variable and the logarithm of BNP, controlling for a linear time trend and individual fixed effects. There was minimal effect of the number of episodes on BNP. However, the impact of hypoxemia is emphasized by the relationship of BNP concentration to both t90 and the difference in SaO_2 between the start and end of each sleep-disordered breathing episode.

The point estimates of BNP responses to sleep-disordered breathing frequency parameters are small, not significant, and are neither consistently positive nor negative (Table 3). For example, the coefficient on the total number of apneas (regression 1) is only 0.002. The standard errors are small enough that we can say with 95% certainty that the true coefficient is <0.0104. Interpreting this clinically, 10 apneas in 20 min—or 30 apneas/h—would increase BNP by <10.4%. The coefficients on the other independent apnea variables are also precisely estimated to be close to zero. Even obstructive apneas (regression 3), which would be expected to cause elevations in BNP from hemodynamic stress, have a point estimate of 0.0037 and an upper bound of 0.0168. Thus, 30 extra obstructive apneas/h would increase BNP at the most by 16.8%.

In contrast to the frequency of sleep-disordered events, nocturnal hypoxemia predicts elevations in BNP. The t90 has a significant positive coefficient of 0.0096, meaning that an extra 10% of the epoch (i.e., 2 min) at low oxygenation increases BNP by 9.6%, with an upper bound of 17.7% and

Figure 1   **Mean BNP and t90**

For each time point through the night, the mean brain (B-type) natriuretic peptide (BNP) of all patients **(solid line)** and the percentage of time with oxygen saturation <90% (t90) **(dashed line)** are shown. Note that the BNP appears to fluctuate with the extent of hypoxemia.

Table 3	Effect of Apneas on BNP		
Regression	**Independent Variable**	**Coefficient**	**95% Confidence Interval**
Frequency parameters			
1	Total number of apneas and hypopneas	0.0020	[−0.0064–0.0104]
2	Number of central apneas	−0.0014	[−0.0185–0.0156]
3	Number of obstructive apneas	0.0037	[−0.0094–0.0168]
4	Number of arousals	−0.0033	[−0.0138–0.0072]
Desaturation parameters			
5	Percent with O_2 saturation <90%	0.0096	[0.0015–0.0177]*
6	Average difference between peak and nadir of O_2 saturation	0.0169	[−0.0100–0.0439]

Each row reports the result of a separate regression of the logarithm of brain (B-type) natriuretic peptide (BNP) on the independent variable specified. Standard errors are clustered by patient-night, of which there were 28 distinct observations. Every regression also includes individual fixed effects and a linear time trend. The sample size is n = 643 for each regression. *p = 0.02.

a lower bound of 1.5%. A similar effect of intermittent desaturation (regression 6) on BNP was observed. Although not statistically significant, the coefficient of 0.0169 indicates that an extra 10 percentage points of average saturation difference increases BNP by 16.9% (95% confidence interval: −10.0% to 43.9%).

We did not detect any significant differences in BNP between nights 2 and 3. The power to compare BNP on night 2 and night 3 is limited by the lack of randomization and the small number of patients. Indeed, baseline log BNP (before oxygen was administered) on night 3 was elevated compared with night 2 (Table 2).

Secondary analyses. There was no latency to a BNP response. The number of sleep-disordered breathing episodes in the preceding 1, 2, 3, 4, or 5 20-min epochs did not predict log BNP (Online Appendix Table 3). Similarly, t90 in preceding epochs generally did not predict log BNP, suggesting that BNP rose contemporaneously with hypoxic exposure (Online Appendix Table 4).

The results of the analysis comparing the effects of central and obstructive sleep apnea are as follows:

Log BNP = 0.0075[−0.0013 to 0.0164]
* predominantly CSA hypoxemia
+ 0.0089[−0.0038 to 0.0217]
* predominantly OSA hypoxemia

The brackets after each coefficient show 95% confidence intervals. A *t* test for equality of the 2 coefficients is unable to reject equality (p = 0.85). Thus, it appears that hypoxemia associated with CSA has the same impact on BNP as hypoxemia associated with OSA.

Discussion

The present study found that in patients with stable HF, changes in BNP during the night were related to the severity of nocturnal hypoxemia, but not to the frequency or type of sleep-disordered breathing episodes or associated arousals. Mechanical and neurohormonal effects of sleep-disordered breathing might be expected to produce hemodynamic stress. Nevertheless, intensive sampling of BNP

showed no relationship between BNP and the frequency of sleep-disordered breathing events or arousals. In contrast, the severity of hypoxemia (defined as percentage of time with an oxygen saturation <90%) did appear to correlate with increased BNP. Few previous studies have separated hypoxia from nonhypoxic arousals and obstruction, and our findings show divergent effects of hypoxic and nonhypoxic episodes. This suggests that sleep-disordered breathing may be detrimental in HF because of hypoxia exerting adverse effects.

Hemodynamic effects of sleep apnea. The interaction between HF and sleep apnea is bidirectional. Hemodynamic disturbances associated with left ventricular dysfunction predispose to periodic breathing and a worsening of sleep apnea (13,14), but there is also evidence that sleep apnea exacerbates HF, and treatment can improve outcomes (5,6). Although apnea has hemodynamic consequences, it is unclear whether these adverse cardiac sequelae are due to the hypoxia that is associated with the apnea or to the direct hemodynamic effects of the apneas.

Upper airway obstruction does increase cardiac pre-load and afterload when dogs inspire repeatedly against an occluded upper airway, but these effects are transient and dissipate during expiration. Perhaps more important are the findings that arousals can exacerbate left ventricular dysfunction by their effects on sympathetic drive, arterial vasoconstriction, and blood pressure (15). Similarly, sleep apnea is associated with recurrent nocturnal surges in blood pressure after each apnea cycle (16). These findings could be secondary to either direct hemodynamic effects or hypoxia. While sleep apnea is clearly associated with hemodynamic changes, the present study suggests that the acute hemodynamic effects of obstructive apnea do not cause elevations in BNP.

Cardiovascular effects of hypoxia. In contrast to the lack of impact of apnea or arousal frequency on BNP, the relationship with hypoxia suggests that mechanisms caused by hypoxia impact cardiovascular function and stress. There is growing evidence that hypoxia is the cause of the cardiovascular effects of sleep apnea. In anesthetized dogs and sedated pigs, investigators have found that the hemo-

dynamic sequelae of sleep apnea are related to the severity of oxyhemoglobin desaturations during apneic episodes (17). The mechanisms might include the negative inotropic effect of hypoxia (18) or the sympathetic drive caused by hypoxia. Hypoxia impairs contractility by altering the action potential which, in turn, interferes with excitation-contraction coupling (19). Hypoxia also leads to a rise in intracellular sodium and calcium, which can be deleterious to the myocytes. Interestingly, in single adult rat myocytes, moderate hypoxia may cause earlier calcium loading and more progressive cell destruction than complete anoxia (20). Hypoxia leads to increased sympathetic activity and arousals at the termination of apneic episodes (21). Moreover, central autonomic responses to intermittent hypoxemia and arousal overwhelm local vasodilatory responses and trigger pronounced sympathetic neural discharge, peripheral vasoconstriction, and increases in blood pressure and cardiac afterload (19).

The association of sleep apnea and hypertension may also be related to hypoxia, rather than arousals. While recurrent arousals increase blood pressure acutely after apneic episodes, blood pressure remains elevated during wakefulness only when nocturnal intermittent hypoxemia is superimposed (22). Indeed, intermittent hypoxemia in combination with arousals may be responsible for the finding in humans that sympathetic nerve activity is elevated in apneic patients compared with weight-, age-, and sex-matched controls (23).

Repeated cycles of hypoxemia followed by reoxygenation triggers the generation of reactive oxygen species and increases oxidative stress (24,25), which, in turn, induces the release of inflammatory cytokines (e.g., tumor necrosis factor-α) (26). These alterations may, in the long term, exacerbate left ventricular dysfunction.

Biomarkers of cardiovascular stress in HF and sleep apnea. BNP, a noninvasive marker of cardiovascular stress, reflects the hemodynamic status and prognosis of HF patients. Numerous studies have demonstrated the relationship between BNP and HF severity (27). Importantly, BNP can acutely reflect changes in hemodynamics. For example, it closely tracked improvement in the pulmonary arterial wedge pressure when HF patients were treated for pulmonary edema (28).

Previous studies of sleep apnea patients suggest that natriuretic peptide concentrations might be affected by sleep apnea and may be impacted by treatment (29–31). In a very small study, OSA appeared to increase atrial natriuretic peptide overnight, but not BNP (32). In contrast, in 22 children, BNP increases overnight correlated with AHI (33). Supporting the findings of the present study, hypoxemia increased the levels of N-terminal proBNP in healthy young men (34), and oxygen therapy decreased BNP concentrations in HF patients with CSA (35). These studies, however, did not look at the cause of decreases in BNP.

Conclusions

Our findings suggest that hypoxia is an important factor in the impact of sleep abnormalities in patients with HF. The present study does not identify whether hypoxia mediates BNP release through direct effects on cardiac contractility, sympathetic nervous system activation, oxidative stress, or other unknown mechanisms. However, the finding that acute changes in BNP are associated with hypoxia rather than apneic episodes suggests a mechanism for the association of sleep abnormalities with HF. Prevention of hypoxia might be especially important in patients with sleep-disordered breathing and HF. A larger sample size and randomized study design will be required to test this hypothesis.

Reprint requests and correspondence: Dr. Stephen S. Gottlieb, University of Maryland, 22 South Greene Street, Baltimore, Maryland 21201. E-mail: sgottlie@medicine.umaryland.edu.

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▶ **APPENDIX**

For the standard methods of evaluating sleep structure and respiratory patterns that were applied to all sleep study recordings, please see the online version of this article.