Brain Natriuretic Peptide in Patients With Congestive Heart Failure and Central Sleep Apnea*

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Study objective: To assess the possible relationship between Cheyne-Stokes respiration (CSR) associated with central sleep apnea (CSA) syndrome and brain natriuretic peptide (BNP) in an outpatient population presenting with stable congestive heart failure (CHF).

Measurements and results: Ninety patients with CHF due to systolic dysfunction (left ventricular ejection fraction \( \leq 45\% \)) were prospectively studied. Each patient underwent conventional polysomnography to establish the diagnosis of CSR-CSA and determination of the BNP level. The correlation between BNP levels and the apnea-hypopnea index (AHI) and desaturation index (DI) was evaluated, as was the accuracy of BNP in identifying CHF-associated CSR-CSA, as determined by the area under the receiver operating characteristic (ROC) curve. Possible confounding variables were assessed, and a stepwise multiple regression analysis was applied to identify those factors that best predicted the variability in BNP levels. Five of the 90 patients were excluded from the study as they presented with obstructive sleep apnea syndrome. Of the remaining 85 patients, 25 (28%) presented with associated CSR-CSA. The mean (SEM) BNP level was higher in this group (166.44 ± 29.6 pg/mL) than in the group with isolated CHF (62.01 ± 13.6 pg/mL; \( p < 0.001 \)). There was a moderate correlation between BNP levels and AHI. The ROC curve that best identified CSR-CSA was obtained with a BNP cutoff value of 116.25 pg/mL (sensitivity, 62%; specificity, 92%; accuracy, 83%). Differences between the two groups in terms of BNP levels persisted after adjusting for the confounding variables that were analyzed. Only AHI and DI were independently related to the BNP level, and both explain the 30.5% variability.

Conclusion: Patients with CHF and CSR-CSA have higher BNP levels than those without CSR-CSA. Our results suggest that CSR-CSA and BNP levels are related. However, the possibility that both factors might be independent expressions of the functional status of CHF patients cannot be ruled out. (CHEST 2005; 127:1667–1673)

Key words: brain natriuretic peptide; central sleep apnea; Cheyne-Stokes respiration; congestive heart failure

Abbreviations: AHI = apnea-hypopnea index; BNP = brain natriuretic peptide; CHF = congestive heart failure; CI = confidence interval; CSA = central sleep apnea syndrome; CSR = Cheyne-Stokes respiration; DI = desaturation index; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ROC = receiver operating characteristic curve; SRBD = sleep-related breathing disorder

Congestive heart failure (CHF) currently constitutes a major health problem in developed Western countries, with a marked socioeconomic impact. Its prevalence has risen in recent years, especially as a consequence of the increased survival rates of patients with acute myocardial infarction.\(^1\)\(^2\) On the other hand, despite the advances in its pharmacologic treatment, CHF continues to be associated with high rates of morbidity and mortality.\(^3\)\(^4\)

The association of sleep-related breathing disorders (SRBDs) with CHF is common, and has been reported to occur in up to 60% of cases in some series. SRBDs can be obstructive apneas (11 to 30%) or, more frequently, Cheyne-Stokes respiration (CSR) with central sleep apnea (CSA) [33 to 41%].\(^5\)\(^6\) CSA is a consequence of the development of CHF but, in turn, appears to have a negative effect on cardiac function.\(^7\) A number of studies\(^8\)\(^–\)\(^11\) have

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demonstrated that patients having CHF associated with CSA present with higher rates of mortality and heart transplantation than patients with CHF but no SRBDs.

The diagnosis of CHF requires relatively complex, and not always available, methods such as echocardiography. The search presently is on for biochemical markers that enable a rapid diagnosis. Brain natriuretic peptide (BNP) is a cardiac neurohormone that is secreted by the ventricles in response to an increase in ventricular volume and pressure overload. The determination of the plasma BNP level has been used for diagnostic purposes since CHF patients usually have higher levels than those presenting with dyspnea of another origin. More-over, several studies have demonstrated that the rise in BNP concentration is proportional to the degree of the severity of cardiac failure, being correlated with the New York Heart Association (NYHA) functional class and, thus, with disease prognosis. Nevertheless, BNP levels can be influenced by other factors such as age, gender, or the presence of renal insufficiency or diabetes. To date, there have been no studies of the possible influence of CSR-CSA on BNP levels in CHF patients. The objective of this study was to assess the possible relationship between CSR-CSA and plasma BNP levels in a population of ambulatory patients with stable CHF.

Materials and Methods

Patients

We performed a prospective study in 90 consecutive patients of both sexes who had CHF due to systolic dysfunction (left ventricular ejection fraction [LVEF] ≤ 45%) and were being treated in the cardiology service of our hospital. All patients were receiving standard drug therapy for their CHF and were clinically stable, a condition defined as the absence of changes in the signs or symptoms of cardiac failure or in the medication dosage within the 4 weeks preceding their enrollment in the study.

The exclusion criteria included the following: (1) instability of CHF during the study; (2) acute myocardial infarction in the previous 3 months; (3) unstable angina; (4) congenital heart disease; (5) daytime PaO₂ of < 60 mm Hg; and (6) treatment with morphine or its derivatives and/or theophylline.

Study Protocol

All of the patients underwent the following tests: (1) answered a specific questionnaire for CHF, including the NYHA functional class, as well as an SRBD-specific questionnaire; (2) underwent echocardiography to determine LVEF; (3) underwent nocturnal polysomnography in the sleep laboratory; and (4) had BNP levels determined by radioimmunoassay. The local committee on ethics approved the study, and written informed consent was obtained from each participant prior to inclusion in the study.

Echocardiography

Echocardiographic studies were performed by a single cardiologist (M.V.-G.) using a digital echocardiographic equipment (Acuson Aspen; Acuson Corporation; Mountain View, CA). Appropriate transducers (3 MHz and 2 MHz) were used to define the cardiac structures. M-mode and two-dimensional echocardiography were performed in the standard views (ie, long-axis, short-axis, apical two-chamber, four-chamber, and subcostal) with the patient in the supine or left lateral position. Measurements were made over three cardiac cycles, and the mean values were obtained. The standard M-mode measurements of internal dimensions at end-diastole were made from the parasternal long-axis view, as recommended by the American Society of Echocardiography. Ventricular dimensions were assessed at the peak of the R-wave of a simultaneous ECG. Fractional shortening, LVEF, and cardiac output were derived from M-mode measurements. Ejection fractions were calculated from the apical four-chamber view using the biplane area-length method.

Polysomnography

The polysomnography consisted of continuous polygraphic recordings for a whole night with standardized equipment (SomnoStar 4100; SensorMedics; Yorba Linda, CA) with surface leads for EEG (ie, C4/A1 and C3/A2), electrooculogram, submental electromyogram, and ECG. Oronasal airflow was detected by thermistors, and the chest and abdominal effort was measured by two belt sensors (Healthdyne Technologies; Marietta, GA). Arterial oxygen saturation was recorded by digital pulse oximeter. All of the recordings were analyzed manually by a pulmonologist (C.C.-B.). The following events were defined: (1) apnea, a complete cessation of oronasal airflow for at least 10 s; (2) hypopnea, a ≥ 50% reduction in the oronasal airflow lasting ≥ 10 s and accompanied by a desaturation and/or an EEG arousal; (3) desaturation, a decrease of at least 4% from baseline in arterial oxygen saturation; and (4) arousal, defined according to the recommendations of the American Sleep Disorders Association. Each apnea and hypopnea was categorized in terms of being obstructive (ie, chest wall and abdominal movements present) and central (ie, chest wall and abdominal movements absent). Sleep data were staged according to the system of Rechtschaffen and Kales. The apnea-hypopnea index (AHI) was defined as the number of apneas-hypopneas per hour of sleep, and the desaturation index (DI) was defined as the number of desaturations per hour of sleep. CSR-CSA was diagnosed when the AHI was ≥ 10 and central apneas represented at least 70% of the total number of respiratory events, together with a characteristic pattern of periodic crescendo-decrescendo in airflow amplitude.

Determination of BNP

The BNP levels were determined by a radioimmunoassay technique (Shionoria BNP; CIS Bio International Diagnostic; Gif-sur-Yvette, France). This sandwich technique uses two different monoclonal antibodies that recognize the carboxy-terminal structure and the intramolecular ring structure of human BNP. In solid-phase assays, one of the antibodies is radiolabeled with 125I and is used as a tracer. In this technique, there is no interaction with other natriuretic peptides. Blood was collected from a peripheral vein in the forearm and introduced into tubes containing ethylenediaminetetraacetic acid (1.5 mg/mL) and aprotonin (500 kallikrein inhibitory units/mL). The blood samples were centrifuged immediately (2,000g) for 5 min to obtain the plasma, which was frozen at -20°C and stored until quantitative BNP analysis was performed.
A descriptive statistical analysis was carried out. The results were expressed as the mean ± SEM, absolute values, and percentages. The quantitative variables were compared using the Student t test for independent samples, and the qualitative variables were studied by the chi² test, using the Fisher exact test when necessary. The level of significance was assumed to be equal to 0.05.

The Pearson product-moment correlation coefficient was employed to determine the strength of the association between BNP levels and the AHI and DI. The accuracy of the BNP level measurement in the identification of CSR-CSA associated with CHF was assessed on the basis of the area under the receiver operating characteristic (ROC) curves. These results were expressed in terms of the area and 95% confidence interval (CI). In addition, the sensitivity, specificity, and positive and negative predictive values were calculated for several cutoff points obtained from the ROC curve.

To adjust the possible confounding variables, analysis of covariance was applied. BNP was considered to be the dependent variable, and the covariables were age, gender, presence of diabetes, renal insufficiency (ie, creatinine level, >2 mg/dL), and LVEF. Stepwise multiple regression analysis was employed to identify those variables that best predicted BNP variability. All of the statistical analyses were carried out using a statistical software package (SPSS for Windows, version 11.5; SPSS; Chicago, IL).

### Results

Five of the 90 patients (6%) were excluded from the study because they were found to have obstructive sleep apneas (AHI ≥10; obstructive apneas-hypopneas representing >30% of all respiratory events). Of the 85 patients with CHF who were finally included in the study, 25 patients (28%) also had CSR-CSA (CHF-CSR-CSA group) with a mean AHI of 30.8 ± 3.4 and a mean DI of 37.2 ± 1.3. The remaining 60 patients (66%) had CHF without any SRBDs associated (CHF-no-SRBD group), and had a mean AHI of 3.17 ± 0.39 and a mean DI of 8.24 ± 4.6.

Patient characteristics are presented in Table 1. The two groups did not differ significantly with respect to gender (although women represented only 4% of the CHF-CSR-CSA group and 15% of CHF-no-SRBD group) or to mean age. There were no differences in the etiology of CHF, although ischemic cardiomyopathy tended to be more common in the CHF-CSR-CSA group than in the CHF-no-SRBD group (52% vs 36.2%, respectively; p = 0.06). The pharmacologic treatment of CHF was similar in the two groups. The LVEF values indicated a moderate-to-severe dysfunction, which also was similar in both groups. The majority of the patients were in NYHA functional class I-II (CHF-no-SRBD patients, 78.4%; CHF-CSR-CSA patients, 76%). Despite the absence of differences in LVEF and NYHA functional class at the time of enrollment in the study, the patients in the CHF-CSR-CSA group had been hospitalized more frequently due to decompensated CHF than those in the CHF-no-SRBD group (96% vs 42.4%, respectively; p < 0.001).

The BNP level was significantly higher in the CHF-CSR-CSA group (166.4 ± 29.6 pg/mL vs 62.01 ± 13.6 pg/mL, respectively; p < 0.001). Figure 1 shows the box plots of the BNP values in each group. There was a moderate correlation between BNP levels and AHI (r = 0.555; p < 0.001) [Fig 2]. The correlation between BNP and DI was also significant (r = 0.503; p < 0.001) [Fig 3].

Figure 4 illustrates the results of ROC curve analysis in which the BNP level was employed to identify CSR-CSA associated with CHF, with an area under the ROC curve of 0.79 (95% CI, 0.668 to 0.913; p < 0.001). Table 2 shows the sensitivity, the specificity, and the positive and negative predictive values for several BNP cutoff values (ie, 80, 116.25, and 152 pg/mL) selected from the ROC curve. The best result was obtained with the cutoff value of 116.25, with a sensitivity of 62%, a specificity of 92%, and an accuracy of 83%. Covariance analysis supported the differences between the two groups of patients in terms of their BNP levels (p = 0.001) after adjusting for age, gender, diabetes, renal insufficiency (ie, creatinine level >2 mg/dL), and LVEF.

In stepwise multiple regression analysis, the 30.5% of variability in BNP levels was predicted by a model that included AHI and DI, with the remaining independent variables (sex, age, LVEF, presence of diabetes, and renal insufficiency) excluded from the model because of a lack of statistical significance.

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### Table 1—Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CHF-no-SRBD</th>
<th>CHF-CSR-CSA</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>54.95 ± 1.5</td>
<td>59.16 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.8 ± 4.8</td>
<td>28.4 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology of heart failure, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>36.2</td>
<td>52</td>
<td>NS</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>44.8</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Others</td>
<td>19</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Oral medications, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>100</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>Digoxin</td>
<td>53</td>
<td>64</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrates</td>
<td>16.7</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>100</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>β-blockers</td>
<td>38.3</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class I–II, %</td>
<td>78.4</td>
<td>76</td>
<td>NS</td>
</tr>
<tr>
<td>History of hospital admissions, %</td>
<td>42.4</td>
<td>96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF, pg/mL</td>
<td>29.5 ± 1.2</td>
<td>29.36 ± 1.59</td>
<td>NS</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>62.01 ± 13.6</td>
<td>166.4 ± 29.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Values given as mean ± SEM or %, unless otherwise indicated. BMI = body mass index; NS = not significant.
Discussion

Our results show that patients with CHF and associated CSR-CSA present higher BNP levels than patients with CHF but without SRBDs. This difference persists after adjustment for age, gender, LVEF, plasma creatinine concentration, and the presence of diabetes. AHI and DI explain 30.5% of the variability in the BNP level. Finally, plasma BNP concentrations show high specificity and negative predictive value for the detection of CSR-CSA in patients with stable CHF.

CHF is a highly prevalent cardiovascular disease (approximately 2% of the population in developed countries)\(^2\) that is associated with elevated rates of morbidity and mortality, despite the advances in pharmacologic treatment with angiotensin-converting enzyme inhibitors and β-blockers.\(^3,4\) At present, it constitutes the most common cause for hospital admission in individuals who are > 65 years of age, and, according to the Framingham Heart Study,\(^2\) the 5-year survival rates are 25% for men and 38% for women. SRBDs are among the factors that could contribute to an unfavorable outcome in patients with CHF. Central apneas are a consequence of the development of CHF but, in turn, are associated with a poor outcome of the latter. This fact could reflect that the patients are in advanced stages of chronic cardiac failure, but it is also possible that SRBDs themselves exert a deleterious effect on cardiac function, probably as a result of the adrenergic activation provoked by the intermittent hypoxemia and arousals associated with apneas.\(^25,26\) In a study by Hanly and Zuberi-Khokhar,\(^9\) the LVEF in CHF patients with CSR-CSA was similar to those who presented with no SRBDs. However, after a follow-up period of between 3 and 4.5 years, the patients with CHF and CSR-CSA presented with higher rates of mortality or heart transplantation than those with isolated CHF, leading the authors to suggest that the association of CSA and CSR constitutes an independent risk factor for mortality. In our cross-sectional study, we have observed no differences between CHF patients with or without associated CSR-CSA in terms of NYHA functional class or LVEF, although there may be indirect data suggesting a greater functional impairment in the former group, since, at the time of enrollment in the study, 96% of them had required hospital admission to treat decompensated CHF vs 42% of the patients with no SRBDs (p < 0.001).
BNP is a cardiac neurohormone that is secreted almost exclusively by the ventricular myocytes in response to ventricular volume expansion and pressure overload. Several studies have found high levels of BNP and an amino-terminal fragment of BNP in patients presenting with symptomatic left ventricular dysfunction, and those levels increase in proportion to the degree of severity of the cardiac failure. BNP levels have been utilized for diagnostic purposes to distinguish patients with CHF from those who present with dyspnea from some other cause. There are also findings that suggest that BNP is a valuable prognostic marker in CHF patients, since it has been observed that raised concentrations of this hormone are associated with elevated rates of hospital admissions, overall mortality, and sudden death.

To our knowledge, to date there have been no studies focusing on the relationship between CSR-CSA and BNP levels in unselected patients with CHF. In a 2003 study carried out in patients with CHF and CSR-CSA, treatment with noninvasive mechanical ventilation was accompanied by a significant reduction in the levels of BNP, a phenomenon that did not occur in the control group. In our series, the patients with CHF and CSR-CSA had mean blood BNP levels that were almost three times higher than those observed in patients with isolated

Table 2—Sensitivity, Specificity, Positive and Negative Predictive Values, and Accuracy for Several BNP Cutoff Values Selected From the ROC Curve

<table>
<thead>
<tr>
<th>BNP, pg/mL</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>67 (46–87)</td>
<td>82 (72–93)</td>
<td>61 (41–81)</td>
<td>86 (76–95)</td>
<td>78</td>
</tr>
<tr>
<td>116.25</td>
<td>62 (41–83)</td>
<td>92 (85–99)</td>
<td>76 (56–97)</td>
<td>85 (76–95)</td>
<td>83</td>
</tr>
<tr>
<td>152</td>
<td>48 (26–69)</td>
<td>94 (88–100)</td>
<td>77 (54–100)</td>
<td>81 (71–91)</td>
<td>80</td>
</tr>
</tbody>
</table>

*Values given as area under ROC curve (95% CI). PPV = positive predictive value; NPV = negative predictive value.
CHF, despite the fact that clinical and functional parameters, such as NYHA functional class and LVEF, were similar in both groups. Moreover, there was a moderate correlation between indexes that express the intensity and severity of CSR-CSA (such as AH1 and DI) and BNP. The analysis of the ROC curves demonstrated that the BNP level had high specificity and negative predictive value for the detection of CSR-CSA (92% and 85%, respectively), although sensitivity was lower (62%).

In the general population, it has been found that the BNP levels (evaluated by means of its N-terminal pro BNP, NT-proBNP) are influenced by age, sex, and other factors. In one study, multiple regression analysis showed that advanced age, female gender, LVEF ≤ 45%, diabetes mellitus, and high plasma creatinine concentrations (among other factors) were independently associated with high plasma NT-proBNP levels. In another study performed in ICU patients, there were no clear differences between the BNP levels in men and women, although the concentrations increased significantly in the latter when those patients who had been admitted to the hospital to undergo treatment for heart disease were excluded. In our series of CHF patients with a mean LVEF of 28 ± 1.02%, analysis of covariance showed that the differences in BNP values in the two groups of CHF patients (those with and without CSR-CSA) persisted after adjusting for the aforementioned variables (p = 0.001). The AH1 and DI were the only two variables related independently to BNP, and both indexes explain its 30.5% variability. The differences between our results and those of Raymond et al could be due to the fact that the populations studied were different. The factors related to BNP in the general population may lose predictive power in patients with conditions like CHF, in which the concentrations of this peptide are higher and other determinants, such as SRBDs, may be present.

The results of our study do not prove that central apneas exert a direct action on BNP production in patients with CHF. The possibility that these two events might be distinct, unrelated expressions of an especially deteriorated cardiac function cannot be ruled out. However, the fact that there is a significant association between AH1 and BNP, independently of other factors that influence the functional class and prognosis of CHF (such as LVEF, age, diabetes, and serum creatinine levels) suggests that, in part, the relationship is direct. This hypothesis agrees with the results of the study of Pepperell et al in which patients with CHF and CSR-CSA treated with noninvasive mechanical ventilation experienced a significant reduction in the serum BNP values that was not correlated with an improvement in the echocardiographic parameters.

CSR-CSA may influence the BNP levels through several mechanisms. Its adrenergic effects may produce cyclic increases in heart rate and arterial BP, and, as a result, may impact on left ventricular afterload. In patients with obstructive sleep apnea syndrome but not CHF, BNP levels have been shown to rise in parallel with arterial BP during sleep. On the other hand, there are data suggesting that hypoxia may exert an independent action on BNP. In patients with chronic respiratory diseases and diurnal hypoxemia (PaO2 < 60 mm Hg), the BNP levels were higher than those of nonhypoxemic patients and healthy control subjects, and decreased significantly after 25 days of home oxygen therapy.

With respect to the characteristics of our series, the rate of CSR-CSA in CHF patients was 28%, which was lower than that reported previously (33 to 40%). This may be due to the fact that we enrolled ambulatory patients who had been studied prospectively and had not been selected for the existence of symptoms suggestive of SRBDs. Moreover, most of our patients (approximately 77%) were in NYHA functional class I or II, and the mean age was somewhat lower than that of patients included in the aforementioned studies. On the other hand, there were no differences in the etiology of CHF when patients with and without CSR-CSA were compared, although ischemic heart disease tended to be more common in those presenting with SRBDs (p = 0.06). In any case, patients with CHF secondary to ischemic heart disease presented with BNP levels similar to those of patients with CHF due to other causes.

In this study, airflow was detected by nasal thermosensors (thermistors), which are less accurate than other methods for measuring nasal airflow. Thus, we have included corroborative data such as desaturation and/or arousal.

In our study, the BNP concentrations were determined using a radioimmunoassay technique (Shionoria BNP; CIS Bio International Diagnostic). This is a slow technique that requires several hours to obtain the results. More rapid methods that provide the results in several minutes are increasingly being employed. There is a good correlation between these techniques when utilized as predictors of the severity of CHF and, thus, the choice of the method for determining BNP does not appear to be, a priori, a limitation of our study.

In conclusion, patients with CHF and CSR-CSA present with higher plasma BNP levels than CHF patients without SRBDs. Although the possibility that central apneas and elevated BNP concentrations independently express an especially deteriorated cardiac function in CHF patients cannot be ruled out, our results suggest that both factors may be related, perhaps through the hypoxia or hemody-
namic changes provoked by CSR-CSA. To clarify this question, studies of the effect of others therapeutic modalities such as noninvasive mechanical ventilation and continuous positive airway pressure on BNP level in patients with CHF, either with or without CSR-CSA, should be carried out.

References