Association Between Plasma Endothelin-1 Levels and Cheyne-Stokes Respiration in Patients With Congestive Heart Failure *

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Study objectives: **Elevated plasma endothelin-1 (ET-1) levels have been reported in association with hypoxia and congestive heart failure (CHF). Furthermore, Cheyne-Stokes respiration-central sleep apnea (CSR-CSA) has been found to correlate with the degree of pulmonary hypertension and the severity of CHF; however, the association between ET-1 levels and CSR-CSA has not been investigated previously.**
Setting: **Veterans Affairs Medical Center.**
Interventions: **We studied 46 consecutive patients with CHF (left ventricular function ≤ 40%) who underwent right-heart catheterization and overnight polysomnography. Thirty-nine patients completed the study. Sixteen patients (41%) had CSR-CSA, 5 patients (13%) had obstructive apnea, and 18 patients (46%) had no sleep-disordered breathing. Circulating plasma ET-1 levels were assayed in patients with CSR-CSA and in patients with no sleep-disordered breathing using commercially available enzyme-linked immunosorbent assay kits.**
Results: **ET-1 levels were significantly elevated in patients with CSR-CSA (mean ± SD, 5.4 ± 1.3 pg/mL) compared to those without central apnea (3.9 ± 1.1 pg/mL; $p < 0.01$), and correlated with mean pulmonary artery pressure ($r = 0.66$, $p < 0.01$), pulmonary capillary wedge pressure ($r = 0.56$, $p < 0.03$), and central apnea frequency ($r = 0.66$, $p < 0.01$). In multivariate analysis, the severity of CSR-CSA was the only variable independently associated with plasma ET-1.**
Conclusions: **We conclude that elevated plasma ET-1 levels are linked to the severity of CSR-CSA. Whether ET-1 represents an important pathogenic factor in CSR-CSA or marker of its occurrence requires further evaluation.** ***(CHEST 2002; 121:1928–1934)***

Key words: Cheyne-Stokes respiration; endothelins; heart failure; hypoxia

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CHF = congestive heart failure; CSR-CSA = Cheyne-Stokes respiration-central sleep apnea; ET-1 = endothelin 1; Ln AHI = natural logarithm of apnea/hypopnea index; LVEF = left ventricular ejection fraction; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance

Heart failure is a common disorder that carries considerable morbidity and mortality despite advances in its treatment.[1–3] A study[4] in patients with chronic, stable heart failure pointed to a high prevalence of periodic breathing during sleep. These breathing disturbances are characterized by recurrent episodes of central apneas (Cheyne Stokes respiration-central sleep apnea [CSR-CSA]) or hypopneas, alternating with hyperpneas during which there is periodic oscillations of tidal volume leading to fluctuation of arterial oxygen saturation, wide variations in intrathoracic pressure, and excessive daytime sleepiness. The presence of CSR-CSA in patients with congestive heart failure (CHF) has been associated with increased pulmonary artery pressure (PAP)[5] and a propensity of ventricular irritability and death.[6,7] The neurohumoral mechanism linking CSR-CSA to mortality has not been fully elucidated, although an increase in sympathetic activity was identified as a potential mediator.[8]

Endothelins are vasoactive peptides with potent

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vasoconstrictor and arrhythmogenic properties produced throughout the cardiovascular system.[9] Elevated plasma concentrations have been reported in patients with depressed left ventricular function, and have been shown to correlate strongly with morbidity and mortality.[10,11] The endothelin system is thought to act in concert with the sympathetic nervous system and the renin-angiotensin-aldosterone system to elevate systemic vascular resistance and constrict the capacitance vessels, thereby elevating afterload and preload of the failing heart. This thesis has been supported by studies in animal models of heart failure that demonstrate the salutary, short-term effect of endothelin-1 (ET-1) receptor antagonists on hemodynamic function and survival with long term administration. Nonetheless, individual neurohormonal factors have not demonstrated specific causality with the extent of pulmonary hypertension in CHF patients with CSR-CSA. This study was performed to investigate the correlation between plasma ET-1 and CSR-CSA in CHF patients with CSR-CSA.

Materials and Methods

Patients

Forty-six male patients with stable CHF due to systolic dysfunction (left ventricular ejection fraction [LVEF] $< 40\%$) were evaluated for participation in the study protocol. All patients were recruited from the cardiology clinics, and were considered for possible heart transplantation. All were receiving optimal oral therapy and were in clinically stable condition at the time of the study (no change in signs or symptoms of heart failure within the previous 6 weeks). At the time of recruitment, no patient had previously undergone a sleep study, and no information was sought about symptoms or risk factors for sleep apnea.

Exclusion criteria included patients with unstable angina, pulmonary edema, congenital heart disease, recent cardiac surgery within the last 6 months, neuromuscular disease, diaphragmatic dysfunction, debilitating stroke with neurologic deficit, and advanced interstitial lung disease, or severe COPD with a forced expiratory volume $< 50\%$ of predicted. Patients who were receiving theophylline or benzodiazepines were also excluded.

The study was approved by the Institutional Review Board and was carried out according to the principles of the Declaration of Helsinki and the institutional guidelines. Patients who were unable to give consent or refused to participate were excluded.

Polysomnography

Continuous EEG, electro-oculography, ECG, and submental and anterior tibial electromyography were recorded on a 16-channel polygraph using standard technique, and digitized on a computerized system (Acquitron; Mallinckrodt; St. Louis, MO). Airflow was measured qualitatively by an oral-nasal thermistor (Graphic Control; Buffalo, NY). Measurement of arterial oxyhemoglobin saturation was performed with a pulse oximeter (Ohmeda 3740; Ohmeda; Boulder, CO), with the probe placed on the patient's finger. Thoracoabdominal movements were recorded using piezoelectric belts.

Sleep stages were scored in 30-s epochs using the Rechtschaffen and Kales sleep scoring criteria.[12] Each epoch was analyzed for the number of apneas, hypopneas, arousals, oxyhemoglobin desaturation, and disturbances in cardiac rate and rhythm. Apneas and hypopneas were scored according to previously published criteria.[8] In brief, a central apnea was defined as an absence of oronasal airflow for ≥ 10 s with no associated movements of the rib cage or the abdomen. An obstructive apnea was defined as the absence of airflow ≥ 10 s in the presence of rib cage and/or abdominal excursions. A hypopnea was defined as a visible reduction in oronasal flow lasting at least 10 s associated with either a 4% decrease in arterial oxygen saturation and or EEG arousal. Hypopneas were classified as central if there was a decrease in chest and abdominal movements and no snoring. Otherwise, hypopneas were classified as obstructive. A mixed apnea was defined as absence of oronasal airflow associated with central followed by obstructive pattern. The presence of CSR-CSA was defined as apnea-hypopnea index (AHI) ≥ 10/h in which $> 75\%$ of events are central in combination with the characteristic pattern of crescendo-decrescendo pattern of hyperpnea alternating with central apnea/hypopneas. Alternately, obstructive sleep apnea was defined as all others with AHI ≥ 10/h, including those with mixed apneas. An arousal was defined as the appearance of waves on the EEG for at least 3 s (EEG). Desaturation index was defined as the number of times the oxygen saturation fell by $\geq 4\%$ from the immediately preceding value for at least 10 s divided by the total sleep time.

Hemodynamic Evaluation

Right-sided heart catheterization was performed using a 7F Swan-Ganz balloon-tipped catheter inserted into the right femoral vein and advanced through the right heart into the pulmonary artery within 3 months of the sleep study. All patients were in clinically stable condition at the time of catheterization. Baseline pulmonary hemodynamic measurements, including systolic PAP, diastolic PAP, pulmonary artery wedge pressure, and mean right atrial pressure, were made with the patients in the supine position, using a transducer (Transpac IV bifurcated monitoring kit, Abbott Critical Care System; Abbott Lab; North Chicago, IL). Cardiac output was measured by the thermodilution method, and the mean of three consecutive measurements was recorded. Pulmonary vascular resistance (PVR) was calculated from the formula (PAP − pulmonary capillary wedge pressure [PCWP])/cardiac output.

Quantitation of Plasma ET-1

Fasting venous blood samples were collected after at least 30 min of supine rest. All blood samples were collected between 8 AM and 10 AM on the day of enrollment to overcome any possible circadian effects. The ET-1 concentrations of human plasma samples were quantified with the use of commercially available sandwich-enzyme immunoassay kit (R&D Systems; Minneapolis, MN) after extraction according to a protocol described previously.[13] All samples and standards were run in duplicate. Former measurements yielded an intra-assay reproducibility of 4.6% ($n = 10$) and an interassay reproducibility of 5.5% ($n = 57$). The sensitivity of the assay was determined at 0.6 pg/mL.

Statistical Analysis

All variables are given as mean ± SD. Differences in means were assessed using the unpaired Student t test. χ^2 analysis with Yates correction was used to analyze proportions. A natural

logarithmic transformation of AHI was used in order to achieve a normal distribution of residuals. To identify relevant relations, regression analysis of sleep-disorder parameters and hemodynamic values with plasma ET-1 was performed. Cook's distance was used to assess for potential outliers.[14] Values > 1 were considered influential. To confirm the observations made by independent regression analysis, we performed a multiple linear regression analysis to select those variables producing the highest partial correlation with plasma ET-1. Pairwise correlations between predictor variables and the variance inflation factor were computed to assess for multicollinearities. A two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using software (SPSS version 10.0; SPSS; Chicago, IL).

Results

Patient Population

Of the 46 patients who were considered eligible for enrollment, 4 patients did not meet the inclusion criteria and 3 patients refused to participate. Five patients had an obstructive AHI ≥ 10/h (range, 14 to 41/h) and were subsequently excluded. Sixteen patients (41%) had documented CSR-CSA, and 18 patients (46%) had a normal sleep study result. The etiology of heart failure was ischemic in all patients. Patient characteristics are shown in Table 1. There were no significant differences in terms of age, body mass index (BMI), LVEF, New York Heart Association functional class, and medical therapy between the CSR-CSA and the non–CSR-CSA group.

Table 2 lists the characteristics of disordered-breathing events and oxyhemoglobin saturation during sleep in the study population. Among patients with CSR-CSA, the mean AHI was 27.2 ± 3.1/h compared to 2.9 ± 1.4/h for non–CSR-CSA patients. As a result, CSR-CSA had significantly more frequent arterial oxyhemoglobin desaturation and an increased number of arousals. Nonetheless, total sleeping time and the proportion of time spent in each stage of sleep did not differ significantly between patients with and without CSR-CSA.

Table 1—*Characteristics of Study Population With and Without CSR-CSA

Characteristics	With CSR-CSA (n = 16)	Without CSR-CSA (n = 18)
Age, yr	67.8 ± 10.8	69.9 ± 11.1
BMI	24.8 ± 2.4	26.8 ± 5.7
NYHA functional class ≥ 3, %	42	37
LVEF, %	26.4 ± 8.5	29.3 ± 9.0
ACE inhibitors	14 (88)	16 (87)
Diuretics	13 (81)	18 (100)
Hydralazine	1 (6)	2 (13)
Digoxin	11 (69)	16 (87)
β-Blockers	2 (12)	2 (11)
Amiodarone	2 (13)	6 (33)

*Data are presented as mean ± SD or No. (%) unless otherwise indicated. NYHA = New York Heart Association; ACE = angiotensin-converting enzyme.

Hemodynamic Correlates of Plasma Endothelin in CHF

The hemodynamic characteristics of the overall population are displayed in Table 3. Mean PAP, PCWP, and PVR were markedly elevated in the CSR-CSA with no significant difference in the cardiac indexes between the two groups. A close and linear relationship was evident between the severity of AHI and the hemodynamic impairment in the CSR-CSA group ($r = 0.75$, $p < 0.001$ for mean PAP, and $r = 0.77$, $p < 0.001$ for PCWP).

In nonapneic subjects, mean plasma ET-1 level was 3.9 ± 1.1 pg/mL (range, 2.4 to 6.1 pg/mL) compared to 5.4 ± 1.3 pg/mL (range, 2.1 to 7.5 pg/mL) [$p = 0.002$] for CSR-CSA (Fig 1). There were significant correlations of ET-1 with mean PAP, PCWP, and PVR in patients with CSR-CSA (Table 4). Similarly, a significant correlation was noted between ET-1 and the natural logarithm of AHI (Ln AHI; Fig 2), and between ET-1 and the desaturation index (Fig 3). The index of determination (r^2) indicated that at least 43% of the variability of the Ln AHI was related to the variability of plasma ET-1 with a correlation of 0.66 ($p = 0.005$). The Cook's distance values for both regressions were < 0.5. To verify the correlation of plasma ET-1 with pulmonary hemodynamic variables and the severity of CSR-CSA, we performed a multivariate regression analysis using variables obtained from the CSR-CSA and the nonapneic group. After eliminating PCWP and PVR to avoid collinearity, three variables (PAP mean, cardiac output, and Ln AHI) remained. With this approach, Ln AHI was the only variable independently associated with plasma ET-1 (Table 5). The overall equation, using these variables, produced a correlation of $r = 0.74$ and $r^2 = 0.54$ with plasma ET-1.

Discussion

Although previous investigators[11] have demonstrated increased circulating ET-1 in patients with CHF and a correlation between ET-1 and left ventricular dysfunction, no work to date has established the relationship between plasma ET-1 and the presence of CSR-CSA in patients with CHF. The present investigation extends current knowledge regarding circulating ET-1 levels in CHF by establishing that circulating ET-1 is raised in CHF patients with CSR-CSA compared to CHF patients without CSR-CSA, and the elevation of plasma ET-1 is

Table 2—*Sleep Characteristics of Patients With and Without CSR-CSA

Characteristics	With CSR-CSA (n = 16)	Without CSR-CSA (n = 18)	p Value
Total dark time, min	351.3 ± 26.4	412.6 ± 19.6	NS
Total sleep time, min	223.8 ± 54.1	288.4 ± 45.2	NS
Sleep efficiency, %	63.7 ± 22.6	69.9 ± 17.6	NS
Sleep stage, % of total sleep time			
1	18.2 ± 4.7	16.5 ± 7.3	NS
2	51.7 ± 2.3	64.1 ± 5.8	NS
3 and 4	3.1 ± 1.6	5.3 ± 3.2	NS
Arousal index, No./h	21.0 ± 4.7	12.6 ± 3.5	0.009
AHI, No./h	27.2 ± 3.1	2.9 ± 1.4	< 0.001
Arterial oxyhemoglobin saturation, %			
Baseline value	92 ± 3	95 ± 4	NS
Lowest value	77 ± 10	89 ± 8	NS
Sleep time < 90% saturation, %	48.2 ± 11.3	1.3 ± 0.4	< 0.001
Desaturation index, No./h	38.4 ± 2.6	1.7 ± 0.8	< 0.001

*Data are presented as mean ± SD. NS = not significant.

positively associated with hemodynamic impairment and the severity of CSR-CSA.

ET-1 Levels in CHF Patients With CSR-CSA

The current data indicate that plasma ET-1 is increased in CHF patients with CSR-CSA, although the range of values demonstrates an overlap between the nonapneic heart failure group and the CSR-CSA group. The difference in plasma endothelin levels between the two groups was not a function of age or BMI, as mean values for the two groups were similar and there was no correlation between age, BMI, and endothelin values for either the patients with CSR-CSA, the nonapneic patients, or for the combined data set.

The correlation between CSR-CSA and pulmonary hemodynamics in our study parallels the observation by Solin and coworkers,[5] who reported an elevated PAP and PCWP in CHF patients with CSR-CSA that correlated proportionally with the severity of apneic events. Moreover, Cody and colleagues[15] demonstrated a significant association between ET-1 and pulmonary hemodynamics, thus raising the possibility of a correlation between ET-1 and CSR-CSA. Our findings provided confirmation to that hypothesis by showing AHI to be the single most important determinant of ET-1.

Albeit the causes of the increase in circulating ET-1 levels in CHF patients with CSR-CSA remains under study, our observation is indicative of either an excessive production or a decreased clearance of ET-1. Simultaneous plasma sampling from various vascular sites in patients with pulmonary hypertension have revealed that systemic arterial ET-1 levels are slightly higher than venous levels,[16] and ET-1 in blood obtained via a pulmonary artery catheter advanced to the capillary wedge position in patients with CHF is increased compared with pulmonary artery levels,[17] suggesting that the pulmonary circulation may contribute to this increase through an increase in production, reduced clearance, or both. Using a porcine model, Kjekshus and coworkers[18] demonstrated that plasma ET-1 was markedly increased because of an augmented release from the

Table 3—*Hemodynamic Indexes of All Participants Grouped According to Respiratory Pattern

Variables	With CSR-CSA (n = 16)	Without CSR-CSA (n = 18)	p Value
Heart rate, beats/min	82 ± 17	79 ± 14	NS
Systemic systolic BP, mm Hg	104 ± 11	109 ± 10	NS
Systemic diastolic BP, mm Hg	60 ± 4	64 ± 3	NS
Systolic PAP, mm Hg	51.3 ± 2.3	32.5 ± 2.1	< 0.001
Diastolic PAP, mm Hg	24.8 ± 1.6	14.3 ± 1.5	< 0.001
Mean PAP, mm Hg	35.9 ± 2.0	21.8 ± 3.8	< 0.001
PCWP, mm Hg	23.6 ± 1.9	14.0 ± 1.2	< 0.001
Cardiac index, L/min/m^2	1.9 ± 0.3	2.2 ± 0.5	NS
PVR, mm Hg/L/min	3.4 ± 0.9	1.7 ± 0.2	< 0.001

*See Table 2 for expansion of abbreviation.

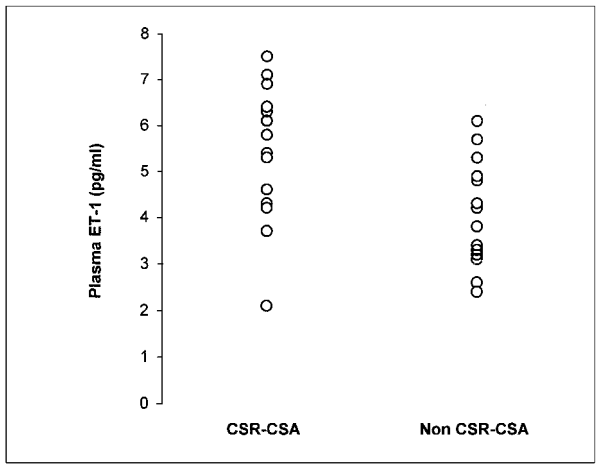

FIGURE 1. Plot shows comparison of plasma ET-1 levels (picograms per milliliter) in CHF patients with CSR-CSA and those without CSR-CSA.

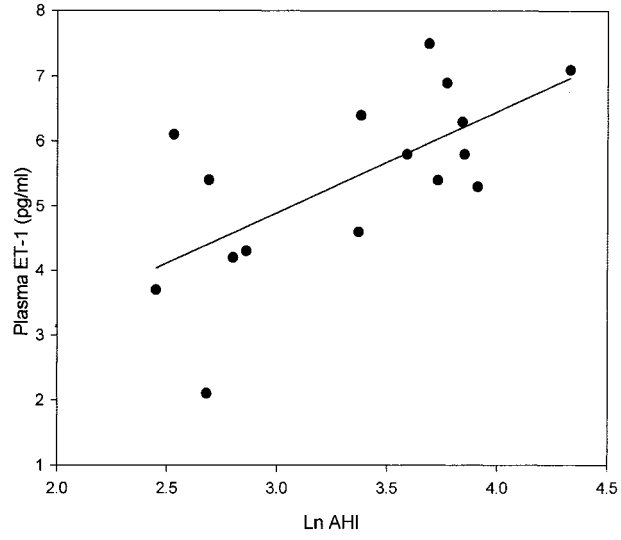

FIGURE 2. Scatter plot showing venous plasma ET-1 levels plotted against Ln AHI. Regression analysis was $y = 0.21 + 1.56x$; $n = 16$; $r = 0.66$; $p = 0.005$.

pulmonary circulation during CHF as the plasma ET-1 rose by sixfold while the endothelin-receptor messenger RNA expression was unaltered and even decreased compared to sham-operated pigs. However, a reduced pulmonary clearance of ET-1 was suggested by the work of Dupuis and colleagues[19] in a rat model with heart failure. Rats with heart failure-related pulmonary hypertension showed a reduction in ET-1 extraction. The reduced clearance was inversely correlated with circulating ET-1 and was associated with the loss of ET-1 gradient across the pulmonary circulation. Irrespective of the mechanism involved in the increase of ET-1, the effect of CSR-CSA on the metabolic properties of the pulmonary vasculature has never been evaluated. Modifications of these properties may not only contribute to an imbalance in the levels of circulating mediators, but to worsening heart failure and probably increased mortality.

Association Between ET-1 and the Severity of CSR-CSA

In the present study, we observed a positive and specific correlation of plasma ET-1 with the severity of Cheyne-Stokes respiration. The relation could be a causal one or may represent an epiphenomenon. A causal relation would mean that repeated Cheyne-Stokes respiration-related hypoxia induces the release of ET-1. Such an interpretation is supported by the following findings: (1) in isolated rat blood vessels and cultured human endothelial cells, hypoxia induces both ET-1 gene expression and secretion of the peptide[20]; (2) the positive correlation between the desaturation index and circulating ET-1 levels shown in this study coincides with the negative correlation between Po_2 and ET-1 plasma levels

Table 4—*Regression Analysis of ET-1 (Ordinate) Pulmonary Hemodynamics and Sleep Parameters (Abscissa) in CHF Patients With CSR-CSA*

Variables	β Coefficient ± SE	F	R^2	p Value
Mean PAP	0.114 ± 0.035	10.73	0.43	0.006
PCWP	0.098 ± 0.039	6.18	0.31	0.026
PVR	0.87 ± 0.32	7.21	0.34	0.017
Desaturation index	0.046 ± 0.016	8.39	0.37	0.011
Ln AHI	1.562 ± 0.479	10.63	0.43	0.005

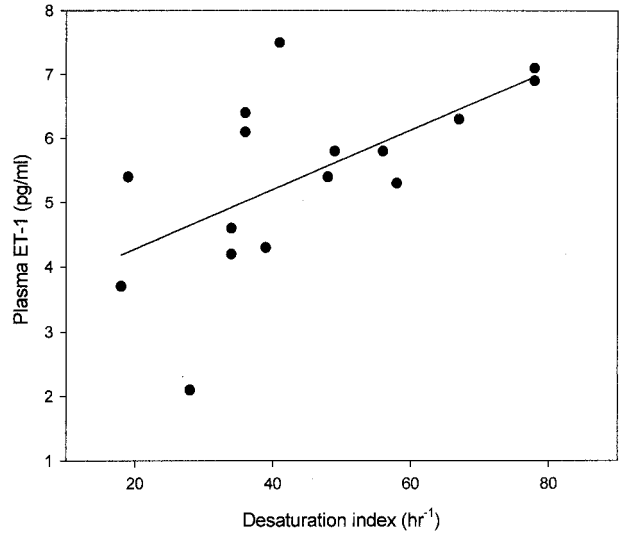

FIGURE 3. Scatter plot showing venous plasma ET-1 levels plotted against the desaturation index. Regression analysis was $y = 3.35 + 0.046x$; $n = 16$; $r = 0.61$; $p = 0.01$.

Table 5—*Multiple Regression Analysis of Hemodynamic Variables and Sleep Parameters That May Influence Plasma ET-1 in the Study Population (n = 34)*

Variables	β-Coefficient ± SE	*t* test Value	p Value
Intercept	0.997 ± 2.387	0.42	0.68
Mean PAP	0.080 ± 0.045	1.80	0.08
Cardiac output	0.064 ± 0.369	0.17	0.86
Ln AHI	0.422 ± 0.202	2.08	0.04

observed in human at high altitude[21]; and (3) a decline in plasma ET-1 levels in response to oxygen breathing was described by Goerre and coworkers,[21] where the decrease of PAP during oxygen administration at high altitude was accompanied by a drop in plasma ET-1 levels. A potential confounding factor might be cigarette smoking, since it might promote further hypoxia. In this study, there was no significant difference in baseline ET-1 levels between smokers and nonsmokers. To the best of our knowledge, no data are available on the effect of cigarette smoking on ET-1 levels.

Another relevant stimulus for ET-1 might be the excess release of catecholamines in patients with CSR-CSA. Naughton and coworkers[8] demonstrated that CHF patients with CSR-CSA have higher overnight urinary norepinephrine and daytime plasma norepinephrine concentrations than patients without CSR-CSA. The concentration of both overnight and daytime norepinephrine was directly related to the degree of apnea-related hypoxia and the frequency of arousals from sleep. There is also evidence in the literature for the stimulation of endothelin secretion from cultured endothelial cells by adrenaline.[22] Specifically, incubation of porcine endothelial cells with epinephrine has resulted in a significant and dose-dependent increase in endothelin secretion.[23] Moreover, the stimulatory effect was blocked by α-adrenergic antagonist phentolamine indicating an α-adrenergic–mediated effect.

Clinical Implications

The significance of this study lies in the prognostic implication of elevated endothelin levels and the beneficial hemodynamic effects of combined endothelin-receptor antagonist and angiotensin-converting enzyme inhibitor therapy in patients with CHF.[24] Current observations might warrant further investigations of the combination therapy in CHF patients with CSR-CSA.

Study Limitations

As is the case for any investigation of therapeutic trials, some potential limitations may have influenced our results. In the absence of esophageal pressure, an inadequate measurement of respiratory effort during sleep can be associated with false diagnosis of central apnea or hypopnea syndrome leading to misclassifications. However, measurement of esophageal pressure is not without drawbacks. It is invasive, often uncomfortable for the patient, and may not be tolerated. Furthermore, there is evidence that an esophageal catheter may modify the pharyngeal airway dynamics,[25] and impair the quality of sleep.[26] Second, we investigated the levels of ET-1 in CSR-CSA in a group of clinically stable CHF patients due to ischemic cardiomyopathy. Our results might not be necessarily applicable to all patients with heart failure. Further investigations should be performed to duplicate these findings in patients with other forms of cardiomyopathies. Third, assessment of CSR-CSA was performed only during a single night of polysomnographic recording, and we did not repeat the test to establish that it persisted after the initial study. Hanley and Zuberi-Khokhar[27] previously reported the persistence of CSR-CSA on repeat either of polysomnography or through a questionnaire obtained from bedpartners of patients with CSR-CSA. Fourth, day-to-day variation of circulating mediators is inherent to most biological systems, and ET-1 levels are potentially subject to these variations. Yet, there has been only one study[28] addressing the circadian cycle of ET-1 in humans with inconclusive results.

Conclusion

In summary, the present study demonstrates a significant correlation between ET-1 and Cheyne-Stokes respiration. Because ET-1 aggravates myocardial injury and affects prognosis, the available data suggest that CSR-CSA is part of a vicious cycle whereby CHF leads to CSR-CSA, which causes hypoxemia, thus inducing a greater activation of the sympathetic nervous system and potentially ET-1, which in turn aggravates heart failure.

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