CHEST

Original Research

SLEEP DISORDERS

Leptin Deficiency Promotes Central Sleep Apnea in Patients With Heart Failure

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Background: **Leptin-deficient animals hyperventilate. Leptin expression by adipocytes is attenuated by atrial natriuretic peptide (ANP). Increased circulating natriuretic peptides (NPs) are associated with an increased risk of central sleep apnea (CSA). This study tested whether serum leptin concentration is inversely correlated to NP concentration and decreased in patients with heart failure (HF) and CSA.**

Methods: **Subjects with HF (N = 29) were studied by measuring leptin, NPs, CO_2 chemosensitivity (Δminute ventilation [$\dot{V}_E$]/Δpartial pressure of end-tidal CO_2 [P_{ETCO_2}]), and ventilatory efficiency ($\dot{V}_E/CO_2$ output [$\dot{V}_{CO_2}$]) and were classified as CSA or no sleep-disordered breathing by polysomnography. CSA was defined as a central apnea-hypopnea index ≥ 15. The Student *t* test, Mann-Whitney *U* test, and logistic regression were used for analysis, and data were summarized as mean ± SD; $P < .05$ was considered significant.**

Results: **Subjects with CSA had higher ANP and brain natriuretic peptide (BNP) concentrations ($P < .05$), $\Delta\dot{V}_E/\Delta P_{ETCO_2}$ (2.39 ± 1.03 L/min/mm Hg vs 1.54 ± 0.35 L/min/mm Hg, $P = .01$), and $\dot{V}_E/\dot{V}_{CO_2}$ (43 ± 9 vs 34 ± 7, $P < .01$) and lower leptin concentrations (8 ± 10.7 ng/mL vs 17.1 ± 8.8 ng/mL, $P < .01$). Logistic regression analysis (adjusted for age, sex, and BMI) demonstrated leptin (OR = 0.07; 95% CI, 0.01-0.71; $P = .04$) and BNP (OR = 4.45; 95% CI, 1.1-17.9; $P = .05$) to be independently associated with CSA.**

Conclusions: **In patients with HF and CSA, leptin concentration is low and is inversely related to NP concentration. Counterregulatory interactions of leptin and NP may be important in ventilatory control in HF.**

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Abbreviations: AHI = apnea-hypopnea index; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CSA = central sleep apnea; HF = heart failure; LVEF = left ventricular ejection fraction; NP = natriuretic peptide; NYHA = New York Heart Association; P_{ETCO_2} = partial pressure of end-tidal CO_2; PSG = polysomnography; $\dot{V}_{CO_2}$ = CO_2 output; $\dot{V}_E$ = minute ventilation; V_T = tidal volume

Central sleep apnea (CSA) is frequent in patients with heart failure (HF) and is caused by abnormal ventilatory control manifest as hyperventilation alternating with compensatory apnea.[1,2] In case series, the frequency of CSA in patients with HF exceeds that of OSA and ranges from 21% to 40%,[3-5] and it has been associated with increased mortality.[6] Unlike patients with OSA, patients with HF and CSA have no upper airway collapse. Indeed, CSA may be considered a consequence of HF and appears to be related to the hemodynamic severity of disease.[7,8] Natriuretic peptides (NPs) are also increased in proportion to the hemodynamic severity of HF, and elevated circulating concentrations have been associated with the presence of CSA.[9,10]

Leptin is an adipokine that regulates food intake and energy expenditure.[11] Since its discovery, leptin has emerged as a pleiotropic hormone studied extensively in the setting of cardiovascular diseases[12-16] and also appears to be important in the regulation of ventilatory control.[14] Human studies of leptin and ventilation have been performed primarily in individuals with OSA[15,16] or obesity hypoventilation syndrome.[17,18] An association of leptin with ventilatory control in patients with HF and CSA has not been reported.

CSA is also associated with increased CO_2 chemosensitivity,[19] as well as hyperventilation at rest and during exercise.[20,21] In vitro studies have shown that atrial natriuretic peptide (ANP) suppresses the secretion of leptin from adipocytes; this may be mediated

via the elevation of cyclic guanosine monophosphate, which activates lipolysis.[22,23] Moreover, leptin-deficient ob/ob knockout mice exhibit increased ventilatory drive, which resolves with leptin replacement.[24] We hypothesized that in patients with HF and CSA, leptin concentration is low and is inversely related to NP concentrations. Accordingly, the aim of this study was to evaluate leptin and NP concentrations in patients with HF and CSA and in patients with HF with no sleep-disordered breathing as demonstrated by polysomnography (PSG).

Materials and Methods

Subject Selection

Subjects were consecutive ambulatory outpatients evaluated in the Mayo Heart Failure Clinic who had left ventricular ejection fraction (LVEF) ≤ 35% and stable HF symptoms (New York Heart Association [NYHA] class II-III) on optimized pharmacotherapy.[25] Clinical stability was defined as no symptom progression and no hospitalization or adjustment of HF therapy in the 3 months preceding enrollment. Exclusion criteria were known sleep apnea or an inability to perform cardiopulmonary exercise testing.

All participants gave written informed consent after being provided a description of the study requirements. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Mayo Clinic institutional review board (IRB 923-02). All procedures followed institutional and Health Insurance Portability and Accountability Act guidelines.

Polysomnography

All PSGs were recorded digitally on either a Network Concepts Incorporated or an E-Series (Compumedics Limited) digital acquisition system. Procedures included four-channel EEG, two-channel electrooculography, submental and limb electromyography, three-channel ECG, transcutaneous pulse oximetry, and thoracic and abdominal inductance plethysmography; other devices used to obtain measurements were a nasal airflow and oronasal thermal sensor, a snore sensor, and a body-position sensor.

All PSGs were scored for sleep stages and disordered breathing events according to 2007 American Academy of Sleep Medicine scoring guidelines.[26] Apneas were defined as a > 90% reduction in the peak airflow signal from baseline, lasting at least 10 s. Hypopneas were defined as a ≥ 30% reduction in the nasal pressure signal excursions from baseline, lasting at least 10 s and accompanied by an oxygen desaturation of ≥ 4% from pre-event baseline. Apneas were classified as central when the apnea criteria were met in the absence of inspiratory effort and as obstructive when the apnea criteria were met despite continued or increased respiratory effort. Patients were considered to have CSA if the total apnea-hypopnea index (AHI) (events/h) was ≥ 15 with ≥ 50% disordered breathing events of central origin, regardless of the presence or absence of respiratory periodicity. Subjects were classified as either (1) CSA or (2) no sleep-disordered breathing by PSG.

CO_2 Chemosensitivity

CO_2 chemosensitivity was measured by a rebreathe technique as described previously.[27] Ventilation was measured breath by breath by pneumotachygraph. Inspiratory gas mixture included 5% CO_2 and balance oxygen at study initiation. Partial pressure of end-tidal oxygen and partial pressure of end-tidal CO_2 (P_{ETCO_2}) were monitored by mass spectroscopy, as were breath-to-breath changes of minute ventilation ($\dot{V}_E$). As subjects rebreathed, inspired CO_2 in the rebreathe bag increased and oxygen fell. Rebreathing continued until P_{ETCO_2} reached 50 to 55 mm Hg. The slope of the plot of the change in $\dot{V}_E$ vs the change in P_{ETCO_2} was used as an index of CO_2 chemosensitivity ($\Delta\dot{V}_E/\Delta P_{ETCO_2}$). Three runs were performed per subject, and values were reported as the mean.

Exercise Testing

The exercise protocol used an initial treadmill speed and grade of 2.0 miles/h and 0%, respectively, with speed and grade increased every 2 min to yield an approximate 2-metabolic equivalent increase per work level to a rating of perceived exertion of 18 to 20 on the Borg scale. Ventilation and gas exchange were assessed by metabolic cart (Medical Graphics Corporation) and included peak oxygen consumption, CO_2 output ($\dot{V}CO_2$), P_{ETCO_2}, tidal volume (V_T), $\dot{V}_E$, and breathing frequency. These data were collected continuously and were reported as averages obtained over the final 30 s of each workload. Derived measures included ventilatory efficiency, defined as $\dot{V}_E/\dot{V}CO_2$.

Leptin, NPs, and Echocardiography

Venous blood was collected on the same day as PSG. Measurement of leptin was performed by radioimmunoassay (LINCO Research Inc), and ANP measurement was performed by radioimmunoassay (Phoenix Pharmaceuticals, Inc). Measurement of brain natriuretic peptide (BNP) was evaluated either by the Shionogi immunoradiometric assay (Shionogi & Co Ltd) or by the DxI 800 immunoassay (Beckman Instruments). All subjects underwent standard, clinically indicated transthoracic echocardiography; measured parameters included LVEF, left ventricle end-diastolic diameter, right ventricular systolic pressure, and left atrial volume.[28]

Statistical Analysis

The Shapiro-Wilk test was used to assess normality. Comparisons between subjects with CSA and without sleep-disordered breathing were made by unpaired Student *t* test or Mann-Whitney *U* test. Differences in proportions were tested by the Fisher exact test, and statistical dependence by the Spearman rank test. Logarithmic transformation was performed for variables with nonnormal distribution. Multivariate logistic regression analysis was

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