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, CO₂ chemosensitivity (Δ minute ventilation [$\dot{V}_E$]/ Δ partial pressure of end-tidal CO₂ [P_{ETCO_2}]), and ventilatory efficiency ($\dot{V}_E$ /CO₂ 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 $\pm$ 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 CO₂; PSG = polysomnography; $\dot{V}_{CO_2}$ = CO₂ output; $\dot{V}_E$ = minute ventilation; VT = 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 CO₂ 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) $\leq 35\%$ 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.

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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 $\geq 30\%$ reduction in the nasal pressure signal excursions from baseline, lasting at least 10 s and accompanied by an oxygen desaturation of $\geq 4\%$ 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 $\geq 50\%$ 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.

CO₂ Chemosensitivity

CO₂ chemosensitivity was measured by a rebreathe technique as described previously.²⁷ Ventilation was measured breath by breath by pneumotachygraph. Inspiratory gas mixture included 5% CO₂ and balance oxygen at study initiation. Partial pressure of end-tidal oxygen and partial pressure of end-tidal CO₂ (PETCO₂) were monitored by mass spectroscopy, as were breath-to-breath changes of minute ventilation ($\dot{V}_E$). As subjects rebreathed, inspired CO₂ in the rebreathe bag increased and oxygen fell. Rebreathing continued until PETCO₂ reached 50 to 55 mm Hg. The slope of the plot of the change in $\dot{V}_E$ vs the change in PETCO₂ was used as an index of CO₂ chemosensitivity ($\Delta\dot{V}_E/\Delta\text{PETCO}_2$). 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, CO₂ output ($\dot{V}\text{CO}_2$), PETCO₂, tidal volume (VT), $\dot{V}_E$, 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 $\dot{V}_E/\dot{V}\text{CO}_2$.

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 non-normal distribution. Multivariate logistic regression analysis was

used to assess the association of CSA with leptin and BNP after controlling for confounders commonly linked to CSA and leptin concentration, such as age, sex, and BMI. Because of the correlation of leptin and BNP with age, sex, and BMI, these variables were used to create a leptin residual. This residual was entered into the model with BNP to assess the simultaneous correlation of both leptin and BNP with CSA. Results were expressed as OR with 95% CI. Log (leptin) and log (BNP) were rescaled to give OR per 1 SD. Data are summarized as mean $\pm$ SD; *P* values $< .05$ were considered statistically significant. Statistical analyses were performed using Statistica 10.0 (StatSoft, Inc) and the Statistical Analysis System (SAS Institute Inc).

RESULTS

Twenty-nine subjects with HF were included in the analysis, including 18 with CSA and 11 with no sleep-disordered breathing (AHI < 5). Subjects with OSA ($n = 11$) or mixed OSA and CSA ($n = 25$) were excluded.

For the subgroups, comparison demonstrated no differences in BMI, LVEF, NYHA class, or mean nocturnal oxygen saturation. There was also no significant difference in left ventricle diastolic dimension (66 ± 8 mm vs 71 ± 10 mm, $P = .21$), right ventricle systolic pressure (42 ± 16 mm Hg vs 48 ± 17 mm Hg, $P = .41$), or creatinine level (1.2 ± 0.3 mg/dL vs 1.4 ± 0.9 mg/dL, $P = .56$). No subject had cardiac resynchronization therapy, and there was no significant difference in the frequency of atrial fibrillation ($P = .27$) between the subgroups. Subjects with CSA were older and mostly men ($n = 15$) and had significantly higher NP concentrations, left atrial volume, and CO_2 chemosensitivity (Table 1).

Leptin concentrations were significantly lower in the CSA group (Fig 1). In the first model, logistic regression analysis demonstrated that leptin (OR = 0.07; 95% CI, 0.01-0.71; $P = .04$) was significantly associated with CSA, and in the second model, BNP (OR = 4.45; 95% CI, 1.1-17.9; $P = .05$) was also independently associated with CSA (age, sex, and BMI adjusted). Univariately, the leptin residual was correlated with CSA (OR = 0.36; 95% CI, 0.14-0.92; $P = .03$) but was no longer significant (leptin residual OR = 0.58; 95% CI, 0.19-1.73; $P = .33$) when BNP was entered into the model (BNP OR = 3.87; 95% CI, 1.03-14.57; $P = .05$). BNP and leptin residual were inversely correlated ($r = -0.55$, $P = .002$). Subjects with CSA also had significantly higher $\dot{V}_E$, higher $\dot{V}_E/\dot{V}_{\text{CO}_2}$, and lower PETCO₂ at rest and during cardiopulmonary exercise testing (Table 2).

Leptin concentration was significantly inversely correlated to the ANP concentration (Fig 2), BNP concentration, left atrial volume, and $\dot{V}_E/\dot{V}_{\text{CO}_2}$ at rest and during exercise, as well as to $\dot{V}_E$ and VT at 50% peak exercise and the severity of CSA by the AHI. Leptin concentration was also significantly and positively correlated with PETCO₂ at rest and during exercise,

and with LVEF. However, there was no correlation between leptin concentration and CO_2 chemosensitivity (Table 3), suggesting that the potential effects of leptin on ventilatory control may not be mediated via direct modulation of chemosensitivity.

DISCUSSION

The novel finding of this study is that individuals with HF and CSA have low leptin concentrations, unlike patients with OSA,²⁹ in whom leptin levels are elevated relative to BMI. Furthermore, leptin concentration inversely correlated with the AHI, indicating a significant relationship between CSA severity and leptin concentration. The logistic regression analysis demonstrated leptin and BNP concentrations to be strongly associated with the presence of CSA in subjects with HF. To our knowledge, our study is the first to implicate leptin in the pathogenesis of CSA and also the first to demonstrate a potentially inhibitory interaction between leptin and NPs in patients with HF and CSA. This apparent counterregulatory relationship^{22,23,30,31} may account for previous reports of low NP levels in obese patients with HF.³²

Our observation that leptin concentration in patients with HF and CSA is low may be attributable to the presence of high ANP and BNP levels and is consistent with *in vitro*^{22,23} and rodent studies^{31,33} that have shown that ANP decreases leptin release from adipocytes. The significantly elevated NPs in our subject cohort are also aligned with previous investigations that found ANP and BNP concentrations to be elevated in patients with HF and CSA.^{9,10}

Subjects with CSA had more severe HF, including evidence of hyperventilation at rest and during exercise, compared with patients with HF without CSA, in agreement with prior report.³⁴ In addition to the relationship between low leptin and CSA, our data showed that leptin concentration was significantly and inversely correlated with $\dot{V}_E/\dot{V}_{\text{CO}_2}$ at rest and during exercise and with $\dot{V}_E$ and VT during exercise, and was positively correlated with rest and exercise PETCO₂. It is noteworthy that a similar breathing pattern has been observed in leptin-deficient ob/ob knockout mice, which ventilate with significantly higher $\dot{V}_E$, VT, and breathing frequency compared with wild-type mice and that this is normalized by leptin replacement.²⁴ However, in contrast to the human subjects with HF in our study, the hypercapnic ventilatory response of ob/ob mice is decreased.^{24,35} Indeed, heightened CO_2 chemosensitivity is a frequent finding in patients with HF,³⁶ and we suggest that the crescendo-decrescendo Cheyne-Stokes breathing pattern of patients with HF and CSA may be caused by the combined effects of increased CO_2 chemosensitivity and leptin deficiency.

Table 1—Subject Characteristics (N = 29)

Parameter	CSA (n = 18)	No Sleep Apnea (n = 11)	P Value
Age, y	67 ± 10	59 ± 10	.04
AHI	39 ± 15	3 ± 3	<.01
Mean nocturnal oxygen saturation, %	94 ± 2	94 ± 2	.94
NYHA class	3 ± 1	2 ± 1	.69
BMI	27 ± 5	27 ± 4	.94
LVEF, %	22 ± 8	26 ± 8	.19
Left atrium volume, mL	123 ± 40	74 ± 20	<.01
ANP, ng/L	4436 ± 2557	2535 ± 1650	.04
BNP, ng/L	919 ± 925	315 ± 445	.03
Leptin, ng/mL	8 ± 10.7	17.1 ± 8.4	<.01
$\Delta\dot{V}_E/\Delta P_{ETCO_2}$, ^a L/min/mm Hg	2.4 ± 1	1.5 ± 0.4	.02
Medications, No. (%)			
ACE-I or ARB	18 (100)	10 (91)	.34
Digoxin	8 (44)	8 (73)	.23
β -Blocker	18 (100)	10 (91)	.34
Diuretics	17 (94)	9 (82)	.54

Data are presented as mean ± SD unless indicated otherwise. ACE = angiotensin-converting enzyme inhibitor; AHI = apnea-hypopnea index; ANP = atrial natriuretic peptide; ARB = angiotensin II receptor blocker; BNP = brain natriuretic peptide; CSA = central sleep apnea; $\Delta\dot{V}_E/\Delta P_{ETCO_2}$ = measure of CO₂ chemosensitivity defined as the slope of the plot of the change in minute ventilation to change in partial pressure of end-tidal CO₂; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

^an = 26.

The relationship between leptin concentration and $\dot{V}_E/\dot{V}_{CO_2}$ in patients with HF has been reported previously. However, in contrast to our findings, Wolk et al³⁷ observed a positive correlation of leptin concentration with $\dot{V}_E/\dot{V}_{CO_2}$. A potential explanation for this apparent discrepancy may be differences in the characteristics of the subjects studied. In the current study,

subjects were more ill, were of a higher NYHA class, and had higher $\dot{V}_E/\dot{V}_{CO_2}$ and lower peak oxygen consumption and greater BNP elevations. We also suggest that the findings of the previous study may have been caused by leptin resistance.³⁸

In our study, there were significantly more men than women in the CSA subgroup, consistent with previous

FIGURE 1. Distribution of mean serum leptin concentrations (ng/mL) in subjects with CSA compared with subjects with no sleep apnea. Mean values with CIs are also shown. CSA = central sleep apnea.

Table 2—Cardiopulmonary Exercise Parameters (N = 29)

Parameter	CSA (n = 18)	No Sleep Apnea (n = 11)	P Value
Rest			
$\dot{V}E$, L/min	14 ± 7	10 ± 3	.03
VT, mL	731 ± 350	567 ± 136	.14
fB, bpm	20 ± 6	18 ± 6	.25
PETCO ₂ , mm Hg	30 ± 4	34 ± 4	.01
$\dot{V}E/\dot{V}CO_2$	49 ± 9	42 ± 6	.03
50% peak exercise			
$\dot{V}E$, L/min	32 ± 12	22 ± 7	.01
VT, mL	1311 ± 482	842 ± 256	<.01
fB, bpm	27 ± 7	27 ± 7	.89
PETCO ₂ , mm Hg	30 ± 6	36 ± 5	.02
$\dot{V}E/\dot{V}CO_2$	42 ± 9	36 ± 7	.05
Peak exercise			
$\dot{V}O_2$, mL/min/kg	15 ± 4	17 ± 6	.45
$\dot{V}E$, L/min	58 ± 20	46 ± 15	.09
VT, mL	1878 ± 667	1412 ± 531	.02
fB, bpm	34 ± 9	34 ± 7	.98
PETCO ₂ , mm Hg	28 ± 6	36 ± 5	<.01
$\dot{V}E/\dot{V}CO_2$	43 ± 9	34 ± 7	<.01

Data are presented as mean ± SD. bpm = breaths per min; fB = breathing frequency; PETCO₂ = partial pressure of end-tidal CO₂; $\dot{V}E$ = minute ventilation; $\dot{V}E/\dot{V}CO_2$ = ventilatory efficiency defined as the ratio of minute ventilation to CO₂ output; $\dot{V}O_2$ = oxygen consumption; VT = tidal volume. See Table 1 legend for expansion of other abbreviation.

reports.⁴ One reason suggested for the consistently lower frequency of CSA in women in reported HF case series has been a lower hypocapnic apnea thresh-

old related to lower levels of testosterone.³⁹ Moreover, circulating testosterone and leptin concentrations are inversely correlated, suggesting that low testosterone levels may contribute to the higher leptin levels observed in women.⁴⁰ We speculate that higher leptin concentrations may protect women against the development of CSA. However, we studied few women and they were less ill, had significantly higher LVEF, and tended to have lower BNP and ANP concentrations, which may have accounted for the higher levels of leptin observed.

Limitations

Our study cohort was small; further studies with greater numbers of subjects, including more women, are necessary to confirm our findings. We did not analyze concentrations of the soluble leptin receptor, which may increase insight into the relationship of leptin concentrations to ventilation.³⁷ We excluded subjects with HF and OSA or mixed apnea with a significant obstructive component because the pathophysiology of these two syndromes is fundamentally different. OSA is characterized by upper airways obstruction, whereas CSA is a consequence of increased ventilatory drive (hyperventilation).⁴¹ Because leptin-deficient animals exhibit increased ventilatory drive, we chose to evaluate whether circulating leptin concentrations were different between a subject cohort with proven CSA and a control group without sleep-disordered

FIGURE 2. Relationship between serum leptin concentration (ng/mL) and ANP concentration in subjects with heart failure. ANP = atrial natriuretic peptide.

Table 3—Associations Between Study Variables and Leptin Concentration (N = 29)

Parameter	Spearman's ρ	P Value
AHI	−0.434	.02
LVEF	0.438	.02
Left atrium volume, mL	−0.670	< .01
50% peak exercise $\dot{V}_E$, L/min	−0.376	.04
50% peak exercise $\dot{V}_T$, mL	−0.418	.02
Rest PETCO ₂ , mm Hg	0.549	< .01
50% peak exercise PETCO ₂ , mm Hg	0.545	< .01
100% peak exercise PETCO ₂ , mm Hg	0.568	< .01
Rest $\dot{V}_E/\dot{V}_{CO_2}$	−0.656	< .01
50% peak exercise $\dot{V}_E/\dot{V}_{CO_2}$	−0.601	< .01
100% peak exercise $\dot{V}_E/\dot{V}_{CO_2}$	−0.541	< .01
ANP, ng/L	−0.602	< .01
BNP, ng/L	−0.627	< .01
$\Delta\dot{V}_E/\Delta\text{PETCO}_{2,a}$ L/min/mm Hg	−0.323	.11

See Table 1 and 2 legends for expansion of abbreviations.

*n = 26.

breathing. Furthermore, leptin levels are known to be elevated in patients with OSA and are frequently associated with leptin resistance,²⁹ and including subjects with OSA in the control group may have brought additional confounders to our study; therefore, using subjects with HF but without sleep-disordered breathing as control subjects seemed most appropriate. To mitigate these limitations, we conducted comprehensive phenotyping of subjects, including complete PSG evaluation of sleep profiles.

CONCLUSIONS

In patients with HF, the circulating leptin concentration is inversely correlated with NP concentrations, suggesting a counterregulatory relationship. Low leptin levels are also associated with hyperventilation at rest, during exercise, and in the presence of CSA in patients with HF, consistent with increased ventilatory drive. Future studies aimed at investigating leptin and NP interactions may be important for further understanding of the pathophysiology of CSA and ventilatory control in patients with HF.

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Dr Cundrle: contributed to the analysis and interpretation of the data and writing of the manuscript.

Dr Somers: contributed to the interpretation of the data and revision of the manuscript.

Dr Singh: contributed to the interpretation of the data and revision of the manuscript.

Dr Johnson: contributed to the interpretation of the data and revision of the manuscript.

Mr Scott: contributed to the statistical analysis, reporting of the data, and writing of the manuscript.

Ms van der Walt: contributed to the interpretation of the data and revision of the manuscript.

Dr Olson: contributed to the planning of the study, interpretation of the data, and writing of the manuscript.

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