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The Relationship between Leptin and Ventilatory Control in Heart Failure Cundrle: Leptin and ventilation in heart failure

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Abstract

Background—Increased serum leptin concentration has been linked to increased ventilation in patients with mild heart failure (HF). However, in animal models the absence of leptin has also been associated with increased ventilation. This study evaluated the relation of circulating leptin concentration to exercise ventilation in HF patients.

Methods and Results—Fifty-eight consecutive ambulatory HF patients were stratified by quintiles of leptin concentration including a lowest quintile of mean leptin concentration of 1.8 ± 0.9 ng/ml and a highest of 33.3 ± 10.3 ng/ml. Peak exercise ventilatory efficiency ($\dot{V}_E/\dot{V}_{CO_2}$) was significantly elevated in the lowest (46 ± 9 vs. 34 ± 6 ; $p < 0.01$) and also in the highest (38 ± 5 vs. 34 ± 6 ; $p < 0.05$) leptin concentration quintiles compared to reference (3^{rd} , middle quintile). Multiple regression analysis adjusted for confounders such as age, gender and BMI showed leptin concentration to be independently inversely correlated to $\dot{V}/\dot{V}_{CO_2}$ in the low-to-normal quintiles ($b = -0.64$; $p < 0.01$), positively in the normal-to-high quintiles ($b = 0.52$; $p = 0.02$) and positively to $P_{ET}CO_2$ in the low-to-normal quintiles ($b = 0.59$; $p = 0.01$) and inversely in the normal-to-high quintiles ($b = -0.53$; $p = 0.02$).

Conclusion—In HF patients, both high and low leptin concentrations are associated with increased $\dot{V}_E/\dot{V}_{CO_2}$ and decreased $P_{ET}CO_2$ with a non-linear U-shaped relation suggesting either leptin deficiency or leptin resistance may modulate ventilatory control in HF patients.

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Keywords

cardiopulmonary exercise testing; ventilatory efficiency; leptin resistance

Introduction

Altered ventilatory control with hyperventilation is frequent in heart failure (HF) patients and associated with more severe symptoms, worse functional capacity (1) and increased mortality (2). Potential causes of hyperventilation include activation of pulmonary J receptors due to congestion, ventilation-perfusion mismatch, increased activation of central and peripheral chemoreflexes and the ergoreflex (1).

Leptin is an adipokine important for the regulation of food intake and energy expenditure (3). Since its discovery leptin has emerged as a pleiotropic hormone with versatile functions in the cardiovascular (4) and respiratory systems (5). Leptin regulatory function has been extensively studied and proposed as a possible link between metabolic, cardiovascular and ventilatory abnormalities in HF (6). Previous investigation has demonstrated that increased circulating leptin concentration is associated with increased minute ventilation per unit of expired carbon dioxide ($V_E/\dot{V}CO_2$) consistent with increased ventilatory drive (6). However, increased ventilatory drive has also been observed in leptin-deficient ob/ob knockout mice (5) and is reversed by administration of leptin (7,8).

The seemingly disparate observations that the absence of leptin in ob/ob knockout mice and elevated leptin concentration in human HF promote increased ventilatory drive suggest that either lack of leptin or leptin resistance may be responsible. By definition leptin resistance requires the presence of increased serum leptin concentration (9). Resistance to the metabolic effects of leptin has been previously described in obese patients (10). Studies of ventilatory control in obese patients have also been consistent with the presence of leptin resistance (11). We hypothesized *that* the relation of leptin concentration to exercise ventilation is non-linear in HF patients and that either leptin deficiency or high leptin serum concentrations are associated with increased ventilatory drive. Accordingly, the aim of this study was to evaluate the relation of serum leptin concentration to exercise ventilation measured in HF patients.

Methods

Subject selection

Subjects were consecutive ambulatory outpatients evaluated in the Mayo Heart Failure Clinic with left ventricular ejection fraction (LVEF) $\geq 35\%$ and stable HF symptoms (NYHA Class I–IV) on optimized pharmacotherapy (12). 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 inability to perform cardiopulmonary exercise testing (CPET).

All participants gave written informed consent after being provided a description of study requirements. The investigation conforms to the principles outlined in the Declaration of

Helsinki and was approved by the Mayo Clinic Institutional Review Board. All procedures followed institutional and Health Insurance Portability and Accountability Act guidelines.

Exercise testing

Functional capacity was assessed by cardiopulmonary exercise testing to volitional fatigue following instrumentation for the measurement of heart rate, metabolic gas exchange and oxygen saturation. The protocol used an initial treadmill speed and grade of 2.0 miles per hour and 0%, respectively, with speed and grade increased every 2 minutes 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. Exercise ventilation and gas exchange were assessed by metabolic cart (Medical Graphics; St. Paul, MN) during cardiopulmonary exercise testing. Measures included peak oxygen consumption, carbon dioxide output, partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$), tidal volume, minute ventilation and breathing frequency. These data were collected continuously and reported as averages obtained over the final 30s of each workload. Derived measures included the ventilatory efficiency defined as the ratio of V_E/VCO_2 . *The V_E/VCO_2 ratio has been shown to strongly correlate with the V_E/VCO_2 slope (1) and may be used to describe ventilatory efficiency at different stages of exercise as well as at rest.*

Leptin, natriuretic peptides and echocardiography

Venous blood for brain natriuretic peptide (BNP) and leptin was collected and measured on the same day as cardiopulmonary exercise testing by commercially available kits. Measurement of plasma leptin was performed by radioimmunoassay (Linco Research Inc., St. Charles, Missouri; intra- and inter-assay variability 3.4% to 8.3% and 3.6% to 6.2%, respectively). Measurement of BNP was evaluated by either the Shionogi immunoradiometric assay (Shionogi & Co, Ltd; Osaka, Japan) or DxI 800 immunoassay (Beckman Instruments; Chaska, Minnesota). The coefficient of variation of these latter two BNP assays was > 0.99. Echocardiography measurements were performed with a focus on cardiac chamber dimensions, left ventricular ejection fraction (LVEF) and stroke volume index.

Statistical analysis

For the evaluation of normally distributed data the Shapiro-Wilk test was used. Subjects were divided into quintiles according to leptin concentration. One-way analysis of variance was used to test for differences among the quintiles, and an unpaired t test or Mann-Whitney U test was used to compare the subject variables between the reference quintile (third) and remaining quintiles. Logarithmic transformation was performed for variables with non-normal distribution. Multiple regression analysis (after controlling for potential confounders such as gender, age, BMI and LVEF) was used to assess the relationship between log leptin concentration and other variables. The results were expressed as the beta coefficient, F ratio and p value. Data are summarized as mean $\pm$ standard deviation (SD); p values <0.05 were considered statistically significant. Statistical analyses were performed using Statistica 10.0 (StatSoft Inc., Czech Republic) and the Statistical Analysis System (SAS Institute Inc., North Carolina).

Results

Fifty-eight HF patients were included in the analysis. Subjects were mostly men (74%), with NYHA functional class III status (57%), low LVEF, low peak exercise oxygen consumption and high BNP (Table 1). For the entire group, leptin concentration was independently positively correlated with body mass index (BMI) ($b=0.52$; $F=27$; $p<0.01$), and inversely with BNP ($b=-0.27$; $F=26$; $p=0.01$) and $\dot{V}_E/\dot{V}CO_2$ ($b=-0.20$; $F=24$; $p=0.03$).

For further comparison, subjects were divided into quintiles according to leptin concentration. The middle (third) quintile with the nearest to physiologic leptin concentration (10.8 ± 2.3 ng/mL) was considered as the reference (13), while the first quintile included subjects with the lowest (1.8 ± 0.9 ng/mL) and the fifth quintile subjects with the highest (33.3 ± 10.3 ng/mL) mean leptin concentrations. Comparison of the clinical characteristics between quintiles is shown in Table 2. When compared with the reference quintile, NYHA class and BNP were significantly higher and BMI and LVEF were significantly lower in the first quintile. NYHA class was also significantly higher in the fifth quintile when compared to the reference third; BMI, stroke volume index, and LVEF were significantly lower and BNP significantly higher in the first quintile than in the fifth quintile.

Exercise ventilation comparisons are shown in Table 3. Peak exercise $\dot{V}_E/\dot{V}CO_2$ was significantly higher (Figure 1) and peak exercise $P_{ET}CO_2$ significantly lower (Figure 2) in the first and fifth quintiles compared to the reference quintile. Peak exercise $\dot{V}_E/\dot{V}CO_2$ was also significantly higher and peak exercise $P_{ET}CO_2$ significantly lower in the first quintile than in the fifth quintile.

Multiple regression analysis adjusted for gender, age, BMI and LVEF was performed for both exercise variables with bi-modal distribution ($\dot{V}_E/\dot{V}CO_2$ and $P_{ET}CO_2$) and separately for low-normal (first-to-third) and normal-high (third-to-fifth) leptin concentration quintiles (Table 4). In the low-to-normal quintiles, $\dot{V}_E/\dot{V}CO_2$ was independently negatively correlated with leptin concentration and positively with BNP level and NYHA class. By contrast, in the normal-to-high quintiles $\dot{V}_E/\dot{V}CO_2$ independently positively correlated with BNP level, NYHA class and leptin concentration. $P_{ET}CO_2$ was also independently positively correlated with leptin and inversely with BNP level and NYHA class in the low-to-normal quintiles while in the normal-to-high quintiles $P_{ET}CO_2$ was inversely correlated with leptin concentration.

Discussion

The major novel finding of this study is that the relation of serum leptin concentration to exercise ventilation in HF patients is non-linear and U-shaped. Low leptin concentrations were significantly inversely and high leptin concentrations significantly positively correlated to increased ventilatory drive as demonstrated by elevated peak exercise $\dot{V}_E/\dot{V}CO_2$ and decreased $P_{ET}CO_2$. We suggest that the negative correlation observed in subjects with low leptin levels is a consequence of leptin deficiency while the positive correlation of leptin concentration to ventilatory drive in subjects with high leptin levels is due to leptin resistance. In addition, leptin concentration positively correlated with BMI and inversely

with BNP concentration, suggesting a potential role of leptin in the BNP obesity paradox of HF patients (14).

The relationship of leptin and ventilatory drive in HF patients has been previously reported by Wolk, et al., (6) who observed elevated $\dot{V}_E/\dot{V}CO_2$ to be associated with increased leptin concentration. We also observed a significant positive correlation of leptin concentration and $\dot{V}_E/\dot{V}CO_2$ in subjects in the normal-to-high leptin quintiles, and our subjects in these quintiles were very similar in regards to clinical characteristics and exercise ventilation to those individuals described in this prior study.

We also observed a significant and independent inverse correlation of leptin concentration and $\dot{V}_E/\dot{V}CO_2$ in our subjects with low leptin concentration consistent with the ob/ob knockout mouse model. These mice, lacking leptin, exhibit increased breathing frequency and minute ventilation before the onset of obesity (5) which is prevented by leptin replacement (7). However, the ob/ob knockout mice are eucapnic or hypercapnic with decreased carbon dioxide chemosensitivity (7,8). In contrast, heightened carbon dioxide chemosensitivity is a frequent finding in HF patients (1) and we suggest that the low $P_{ET}CO_2$ observed in our subjects may be due to the combined effects of increased carbon dioxide chemosensitivity, leptin deficiency and lean body habitus.

The positive correlation of leptin and ventilatory drive observed by Wolk, et al., (6) and in our subjects in the upper leptin quintiles may be accounted for by leptin resistance. Resistance to the metabolic effects of leptin has been previously described in obese patients (10). The existence of leptin resistance for the respiratory system has been proposed in an animal model by O'Donnell, et al., (15) and by others in obese patients (11) and in obese patients with obstructive sleep apnea (16).

Leptin has been shown to have potentially beneficial as well as adverse effects in the cardiovascular system (17). Based on our observations, either the lack of leptin or the relative lack of leptin (i.e., leptin resistance) promotes increased $\dot{V}_E/\dot{V}CO_2$. Elevated $\dot{V}_E/\dot{V}CO_2$ has been found to be associated with increased morbidity and adverse prognosis in HF patients (2). It has been suggested that the association between serum leptin concentration and $\dot{V}_E/\dot{V}CO_2$ may contribute, in part, to the adverse prognostic implications of increased $\dot{V}_E/\dot{V}CO_2$ (6).

In our study, the proportion of women increased with the increase of leptin concentration. This is consistent with prior reports which have demonstrated women to have significantly higher leptin concentrations (18). It has been shown that healthy women have significantly lower $P_{ET}CO_2$ and higher $\dot{V}_E/\dot{V}CO_2$ (19), and in women with HF $\dot{V}_E/\dot{V}CO_2$ has been shown to be higher than in men (20). Notably, the serum leptin concentration and $\dot{V}_E/\dot{V}CO_2$ or $P_{ET}CO_2$ relation observed in this study was significant even after controlling for sex.

In our study, circulating leptin concentration was also independently inversely correlated with BNP concentration. Our observations are consistent with previous in-vitro (21) and rodent studies (22) which have shown that natriuretic peptides decrease leptin release from adipocytes. Furthermore, BNP has been recently found to act as a strong lipolytic factor (23), which promotes cardiac cachexia (24), and lowers total body fat and leptin production

(25). However, increased leptin has also been found to decrease natriuretic peptide concentrations (22) suggesting that leptin and natriuretic peptides may be counter-regulatory. The mechanism of the BNP obesity paradox has not yet been elucidated (14). The positive correlation of serum leptin concentration and BMI in our study is consistent with previous reports (26) and taken together with the observation of an inverse correlation between leptin and BNP concentrations suggests increased leptin in obese patients with HF may promote decreased BNP (27). Further mechanistic studies are needed to clarify this potential relationship.

A limitation of our study was that we did not analyze concentrations of the soluble leptin receptor which may provide additional insight into the relationship of leptin concentrations to ventilation (6). *Stratification to quintiles allowed us to demonstrate the “U shaped” relation of leptin and ventilatory drive ($V_E/V\dot{CO}_2$ and $P_{ET}CO_2$). However, it also produced smaller groups for statistical comparison, which could have caused overestimation of the significance of our findings.* In mitigation, the strength of our study lies in the study population which encompasses the entire clinical spectrum for both circulating leptin concentration and severity of HF. *Another statistical limitation was that the multiple regression analysis was adjusted for BMI which may underestimate the proportion of body fat (28). We did not estimate the percentage of body fat and so were unable to include this measure in the analysis. However, it has been shown that both BMI and the percentage of body fat strongly correlate with leptin concentrations (26).*

In conclusion, in HF patients, either high or low leptin concentrations are associated with increased $V_E/V\dot{CO}_2$ and decreased $P_{ET}CO_2$ and demonstrated a non-linear U-shaped relation which may be caused by either deficient leptin or leptin resistance which may modulate ventilatory control. Increased circulating leptin levels may also contribute to the low BNP concentrations observed in HF patients with high BMI and promote the obesity paradox of HF.

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Figure 1.

Peak exercise ventilatory efficiency by quintiles. Peak exercise ventilatory efficiency ($V_E/\dot{V}CO_2$) was significantly higher in the first and fifth quintiles compared to the reference quintile demonstrating a U-shaped relation.

Figure 2.

Peak exercise end-tidal carbon dioxide pressure by quintiles. Peak exercise endtidal carbon dioxide pressure ($P_{ET}CO_2$) was significantly lower in the first and fifth quintiles compared to the reference third quintile demonstrating an inverse U-shaped relation.

Table 1

Clinical characteristics (n=58)

Age (<i>years</i>)	65 ± 10
Male gender No. (%)	43 (74%)
BMI (kg/m^2)	28 ± 5
NYHA class I/II/III/IV No. (%)	14 (24)/9 (16)/33 (57)/2 (3)
SVI (mL/m^2) (n=57)	40 ± 11
LVEF (%)	26 ± 9
peak $\dot{\text{V}}\text{O}_2/\text{kg}$ (mL/kg)	15.7 ± 4.7
peak $\dot{\text{V}}_{\text{E}}/\dot{\text{V}}\text{CO}_2$	39 ± 8
BNP (ng/L)	660 ± 804
Leptin (ng/mL)	13.4 ± 11.8

BMI = body mass index; cc = cubic centimeter; kg = kilogram; min = minute; ng = nanogram; NYHA = New York Heart Association Class; L= liter; LAV = left atrial volume; LVEF = left ventricular ejection fraction; m^2 = square meter; mL = milliliter; SVI = stroke volume index

Table 2

Clinical Characteristics by Leptin Quintile

Parameter	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	ANOVA p
Male gender (%)	n=12 100	n=12 92	n=11 73	n=12 75	n=11 27§	<0.01
Age (years)	63 ± 13	69 ± 9	66 ± 13	67 ± 8	59 ± 7	0.21
BMI (kg/m ²)	24 ± 3*	27 ± 4§	29 ± 5§	29 ± 4§	32 ± 6§	<0.01
NYHA class	3 ± 1*	2 ± 1	2 ± 1§	2 ± 1	3 ± 1*	0.05
SVI (mL/m ²)	32 ± 12	41 ± 10	37 ± 7	46 ± 4*§	47 ± 14§	<0.01
LVEF (%)	19 ± 7*	26 ± 7§	27 ± 8§	27 ± 7§	30 ± 14§	0.03
BNP (ng/L)	1513 ± 1166*	764 ± 743	396 ± 337§	250 ± 341§	326 ± 215§	<0.01
Leptin (ng/mL)	1.8 ± 0.9*	6.1 ± 1.0*	10.8 ± 2.3	16.9 ± 1.5*	33.3 ± 10.3*§	<0.01
(range)	(0 – 3.4)	(3.5 – 7.5)	(7.6 – 14.4)	(14.5 – 18.8)	(18.9 – 48.8)	

* p< 0.05 (compared to reference quintile)

§ p< 0.05 (compared to lowest quintile)

BMI = body mass index; BNP = brain natriuretic peptide; cc = cubic centimeter; kg = kilogram; L = liter; LVEF = left ventricular ejection fraction; min = minute; m² = square meter; mL = milliliter; ng = nanogram; NYHA = New York Heart Association Class; SVI = stroke volume index

Table 3

Exercise Parameters by Leptin Quintile

parameter	Quintile 1 n=12	Quintile 2 n=12	Quintile 3 n=11	Quintile 4 n=12	Quintile 5 n=11	p
rest						
$\dot{V}O_2$ (mL/min/kg)	3.4 ± 0.9	4.3 ± 1.4	4.3 ± 0.7	4.2 ± 0.7	3.6 ± 1.2	0.08
$\dot{V}_E$ (L/min)	10 ± 3*	15 ± 5 [§]	13 ± 5	13 ± 3 [§]	11 ± 4	0.04
V_T (mL)	564 ± 144	710 ± 194	870 ± 462	737 ± 192	718 ± 239	0.12
f_b (bpm)	18 ± 3	22 ± 6*	17 ± 5	18 ± 5	16 ± 5	0.03
$P_{ET}CO_2$ (mmHg)	31 ± 4	31 ± 3	34 ± 4	35 ± 5 [§]	33 ± 3	0.04
$\dot{V}_E/\dot{V}CO_2$	50 ± 9*	48 ± 13	41 ± 5 [§]	41 ± 5 [§]	40 ± 3 [§]	0.02
Peak exercise						
$\dot{V}O_2$ (mL/min/kg)	14.4 ± 5.2	15.3 ± 4.2	17.1 ± 3.7	18.2 ± 6.0	13.3 ± 2.2	0.07
$\dot{V}_E$ (L/min)	50 ± 22	59 ± 19	51 ± 26	61 ± 15	49 ± 12	0.28
V_T (mL)	1696 ± 641	1736 ± 424	1794 ± 781	1605 ± 702	1493 ± 431	0.73
f_b (bpm)	32 ± 8	34 ± 9	31 ± 8	34 ± 8	33 ± 5	0.76
$P_{ET}CO_2$ (mmHg)	28 ± 7*	30 ± 6*	35 ± 4 [§]	35 ± 5 [§]	31 ± 4* [§]	<0.01
$\dot{V}_E/\dot{V}CO_2$	46 ± 9*	41 ± 10	34 ± 6 [§]	36 ± 7 [§]	38 ± 5* [§]	0.01

* p<0.05 (compared to reference third quintile)

[§] p<0.05 (compared to lowest first quintile)

bpm = breaths per minute; CSA = central sleep apnea; f_b = breathing frequency; kg = kilogram; L = liter; min = minute; mL = milliliter; mmHg = millimeters of mercury; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide; $\dot{V}_E$ = minute ventilation; $\dot{V}_E/\dot{V}CO_2$ = ventilatory efficiency; $\dot{V}O_2$ = oxygen consumption; V_T = tidal volume

Table 4

Multiple regression analysis

		1 st – 3 rd Quintile		3 rd – 5 th Quintile	
		b	F	b	F
peak exercise $\dot{V}_{E'}/\dot{V}CO_2$	leptin	-0.64	4.2	0.52	3.2
	BNP	0.61	5	0.38	2.9
	NYHA	0.58	5.9	0.49	3.7
	SVI	-0.29	2.5	0.16	1.9
peak exercise $P_{ET}CO_2$	leptin	0.59	3.6	-0.53	3.1
	BNP	-0.56	4.2	-0.35	2.6
	NYHA	-0.52	4.7	-0.33	2.4
	SVI	0.34	2.6	-0.11	1.7

First-third Quintile = low and normal leptin concentration; Third to fifth Quintiles = normal and high leptin concentration; B = beta coefficient; BNP = brain natriuretic peptide; F = F ratio; NYHA = New York Heart Association Class; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide; SVI = stroke volume index; $\dot{V}_{E'}/\dot{V}CO_2$ = ventilatory efficiency.