Leptin, a Novel Predictor of Lung Function in Heart Failure*

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Background: **Leptin is a protein hormone produced by adipose tissue. Leptin has proinflammatory properties and is usually elevated in patients with chronic heart failure. We assessed if serum leptin relates to the loss in lung function in noncachectic patients with chronic heart failure.**
Materials and methods: **One hundred thirty-five consecutively eligible non-Hispanic white subjects (age, 24 to 79 years; 85 men and 50 women) with a diagnosis of stable systolic heart failure were recruited prospectively, along with 106 matched control subjects. FVC, FEV_1, and single-breath diffusing capacity of the lung for carbon monoxide (DLCO) were measured by spirometry. Plasma leptin was measured by radioimmunoassay. Multiple linear regression was applied.**
Results: **The relationships of FEV_1, FVC, and DLCO with leptin differed significantly between heart failure and control subjects after controlling for age, sex, percentage of body fat, and ejection fraction. In heart failure, leptin was as an independent predictor of FVC values (additional $R^2 = 0.05$, $p < 0.0001$), FEV_1 values (additional $R^2 = 0.05$, $p < 0.0001$), and DLCO values (additional $R^2 = 0.14$, $p < 0.0001$). In a final multiple regression model predicting lung function in heart failure, the independent effect of leptin was significant after further adjustments.**
Conclusions: **The predictive information provided by leptin is additive to that provided by measures of body fat in heart failure patients, especially for DLCO. Leptin may play a role in the impairment of lung function in subjects with heart failure.** ***(CHEST 2008; 134:346–350)***

Key words: body fat; heart failure; leptin; lung

Abbreviations: BMI = body mass index; BNP = brain natriuretic peptide; DLCO = diffusing capacity of the lung for carbon monoxide; EF = ejection fraction; LogLeptin = log-tranformed leptin; NYHA = New York Heart Association

Leptin, a protein hormone produced by adipose tissue, has proinflammatory properties.[1] Leptin exerts its biological actions through binding to its receptors that are found in a variety of tissues. There are at least six isoforms of this receptor, one of which, the Ob-Rb isoform, is considered to be the longest and fully functional.[2] A study[2] that surveyed the distribution of leptin receptors in different tissues has demonstrated that the epithelial cells of the adult lung displays particularly high levels of the functional leptin receptor (Ob-Rb). Leptin may exacerbate existing lung inflammation, contributing to the poor clinical outcomes of subjects with lung diseases.[4] It has been suggested that leptin may play a pivotal role in obesity-related breathing disorders.[5]

Metabolic abnormalities in heart failure include local and systemic paracrine-endocrine systems that lead to an imbalance between catabolic and anabolic mechanisms. In noncachectic patients with heart failure, increased circulating levels of catecholamines, and systemic and local activation of proinflammatory cytokines have been described and linked to worse clinical outcome and mortality.[6,7] Elevated systemic levels of leptin and its receptor have been described in patients with heart failure independently of obesity.[8] Hyperleptinemia also correlates to serum levels of proinflammatory cytokines such as tumor necrosis factor-α.[9]

Diffusing capacity is a measurement of carbon monoxide transfer from inspired gas to pulmonary capillary blood. During the test, the subject inspires a gas containing carbon monoxide and one or more tracer gases to allow determination of the gas-exchanging capability of the lungs. Given that patients with heart failure often have obstructive and restrictive changes in

baseline pulmonary function along with reductions in the diffusing capacity of the lung for carbon monoxide (DLCO), it is relevant to identify the mechanisms responsible for the loss of lung function in this population, such as the possible role of inflammation.

The aim of the present study was to assess if serum leptin contributes to the prediction of lung function assessed by spirometry (namely, FVC, FEV_1, and DLCO) in noncachectic heart failure subjects. This study was undertaken to assess the degree to which lung function measures may be explained by serum leptin in heart failure.

Materials and Methods

Subjects

One hundred thirty-five consecutively eligible white patients with a diagnosis of stable noncachectic systolic heart failure were recruited prospectively at the Mayo Clinic, Rochester, MN. Cardiac cachexia was defined as a body weight < 85% of ideal. The etiology of heart failure was ischemic or nonischemic dilated cardiomyopathy. Patients with conditions likely to influence pulmonary function test results independent of heart failure (primary lung disease, obesity, musculoskeletal diseases, peripheral vascular disease, chest pain, pacemaker dependency, atrial fibrillation, COPD), valvular heart disease, history of complex ventricular arrhythmias, or with a moderate smoking history were excluded. The clinical characteristics of the study group are shown in Table 1. The study was approved by the Mayo Institutional Review Board. Informed consent was obtained before participation.

Protocol

All subjects underwent anthropometric measurements (including assessment of percentage of body fat[10,11] and body mass index [BMI]) and pulmonary function tests. Pulmonary function measurements were performed at rest and included an assessment of FVC and FEV_1. A single-breath DLCO was also measured. Spirometry and DLCO data were collected in accordance with the American Thoracic Society standards.[12] DLCO was adjusted for hemoglobin levels.

Blood samples were drawn at rest in a supine position in the morning after an overnight fast. Leptin was measured by radioimmunoassay (Linco Research; St. Charles, MO) [intraassay and interassay variability, 3.4% to 8.3% and 3.6% to 6.2%, respectively]. Brain natriuretic peptide (BNP) was measured by immunoradiometric assay (Shionogi; Osaka, Japan) [interassay and intraassay variability were both 8%], and angiotensin II was measured using a nonequilibrium assay (Phoenix Pharmaceuticals; Belmont, CA) [interassay and intraassay variations were 13% and 9%, respectively].

Table 1—*Descriptive Characteristics in 149 Men and 92 Women

Characteristics	Control Subjects (n = 106)	Heart Failure (n = 135)
Age, yr	53.8 ± 15	55.5 ± 11
Female gender	42 (40)	50 (36)
BMI, kg/m^2	24.9 ± 3	28.2 ± 5†
Percentage of body fat	23.8 ± 7	27.2 ± 7†
EF, %	62.6 ± 7	29.03 ± 11†
Angiotensin II, pg/mL	7.7 ± 16	14.3 ± 19†
BNP, pg/mL	42.7 ± 147	489 ± 423†
Leptin, ng/mL	7.6 ± 6	13.2 ± 12†
Pulmonary function		
FVC % predicted	106 ± 14	86.7 ± 17†
FEV_1 % predicted	104 ± 14	84.4 ± 18†
DLCO % predicted	96.7 ± 14	82.6 ± 16†

*Data are presented as mean ± SD or No. (%).
†Statistical significance ($p < 0.01$) for differences between heart failure and control subjects.

Statistical Analysis

Data were summarized by calculating means and SD for quantitative variables and percentages for categorical variables. Due to skewness, leptin was log transformed (log-transformed leptin [LogLeptin]). Linear regression modeling was used to assess the simple and joint associations of FVC, FEV_1, and DLCO (expressed in percentage of predicted values) and LogLeptin, adjusting for percentage of body fat, which was always included as a covariate in the models. Percentage of predicted values are already adjusted for age, height, and gender per equation. Then parsimonious multiple regression models were constructed from each of the FVC, FEV_1, and DLCO (expressed as percentage of predicted), using forward stepwise selection to assess whether serum leptin made an additional contribution to the prediction of lung function. In all stepwise regression analyses, strict variable entry ($p < 0.10$) and elimination criteria ($p < 0.05$) were applied after forcing age and sex in the models. The predictive value of each set of measures was assessed by comparing R^2 values of the models obtained from each set.

Results

Descriptive Characteristics

The age and gender mix did not differ significantly between heart failure patients and control subjects;

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