

Obesity and Suppressed B-Type Natriuretic Peptide Levels in Heart Failure

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OBJECTIVES	This investigation evaluated the relationship between obesity and B-type natriuretic peptide (BNP) in heart failure.
BACKGROUND	Obesity is a major risk factor for the development of heart failure, but the precise mechanisms remain uncertain. Physiologically, natriuretic peptides and lipolysis are closely linked.
METHODS	A total of 318 patients with heart failure were evaluated between June 2001 and June 2002. Levels of BNP were compared in obese (body mass index [BMI] ≥ 30 kg/m ²) and nonobese (BMI < 30 kg/m ²) patients with respect to New York Heart Association functional class and lean body weight-adjusted peak aerobic oxygen consumption. In a subset of 36 patients, plasma levels of tumor necrosis factor- α , interleukin-6, and soluble intercellular adhesion molecule-1 were measured.
RESULTS	The population's BMI was 29.4 ± 6.6 kg/m ² ; 24% were lean (BMI < 25 kg/m ²), 31% overweight (BMI ≥ 25 to 29.9 kg/m ²), and 45% obese (BMI ≥ 30 kg/m ²). Obese patients were younger, more often African American, and more likely to have a history of antecedent hypertension, but less likely to have coronary artery disease and with only a trend toward diabetes mellitus. Levels of BNP were significantly lower in obese than in nonobese subjects (205 ± 22 and 335 ± 39 pg/ml, respectively; $p = 0.0007$), despite a similar severity of heart failure and cytokine levels. Multivariate regression analysis identified BMI as an independent negative correlate of BNP level. There were no differences in emergency department visits, heart failure hospitalization, or death between the obese and nonobese patients at 12-month follow-up.
CONCLUSIONS	Our investigation indicates that a state of reduced natriuretic peptide level exists in the obese individual with heart failure. (J Am Coll Cardiol 2004;43:1590-5) © 2004 by the American College of Cardiology Foundation

The role of natriuretic peptides in the clinical expression of chronic heart failure (CHF) has been established (1). Contemporary investigations have correlated the levels of circulating B-type natriuretic peptide (BNP) with the severity of heart failure, and it can provide incremental refinement for improving the diagnosis of heart failure (1,2). Other studies have alluded to variations in the expression of this hormone as a function of age, gender, and renal dysfunction (3,4).

The influence of obesity on the development of cardiovascular disease has also been well established (5). In particular, obesity is a known factor that has an impact on systolic and diastolic ventricular function and has also been identified as a major risk factor for the development of coronary artery disease and heart failure (6-8). Physiologically, natriuretic peptides and lipolysis have been closely linked, and adipose tissues are intimately related to the natriuretic clearance receptor (9,10). Hence, this raises the possibility that the pathophysiologic mechanisms underlying the relationship between obesity and cardiovascular

disease outcomes could at least partially be related to the impact of natriuretic peptides (9,10).

Therefore, we hypothesized that the state of obesity and heart failure could be associated with alterations in the peripheral expression of natriuretic peptides. Thus, this investigation was designed to evaluate the relationship between obesity and circulating levels of BNP.

METHODS

Study design. A total of 318 patients with CHF were evaluated in our heart failure center between June 2001 and June 2002. All patients received a careful history and physical examination by a heart failure specialist physician who was blinded to BNP data. To be included in this analysis, patients had to have CHF (with or without obesity) for at least six months and receive stable doses of their medications with no recent increases in symptoms or the need for intravenous medication support for at least six weeks before evaluation. Thus, this cohort did not selectively comprise those with obesity-induced heart failure. Those patients with an acute coronary syndrome, new-onset atrial arrhythmia, percutaneous or surgical coronary revascularization or other cardiac surgery, or severe renal dysfunction (serum creatinine > 3.0 mg/dl or current dialysis) within the previous three months were likewise excluded. The severity of CHF was categorized by New York Heart Association (NYHA) functional class criteria, as well as by

From the Department of Cardiovascular Medicine, Ochsner Clinic Foundation, New Orleans, Louisiana. Dr. Mehra has served as a consultant to Biosite Diagnostics, Inc., the makers of the BNP assay used in this study. However, this potential conflict has in no way biased the author's viewpoint. Dr. Mitchell Finkel acted as Guest Editor of this paper.

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Abbreviations and Acronyms

BMI	=	body mass index
BNP	=	B-type natriuretic peptide
CHF	=	chronic heart failure
CI	=	confidence interval
CPX	=	cardiopulmonary stress testing
LV	=	left ventricular
LVEF	=	left ventricular ejection fraction
NYHA	=	New York Heart Association
VO ₂	=	oxygen consumption

performance of cardiopulmonary stress testing (CPX) in order to establish peak aerobic capacity in all patients. Detailed demographic variables and clinical data were collected at the time of study performance. Additionally, a subgroup of patients underwent evaluation of pro-inflammatory cytokines in order to assess the status of CHF with BNP levels and obesity. Our Institutional Review Board approved the study.

Measurement of BNP. The bioactive BNP level was analyzed at the time of clinical assessment. For each BNP measurement, 5 ml of whole blood was collected into tubes containing potassium EDTA (1 mg/ml blood) and measured using the Triage BNP test (Biosite Diagnostics Inc., San Diego, California). This test is a fluorescence immunoassay for the quantitative determination of BNP in whole blood and plasma specimens. The turnaround time for the assay is 15 to 20 min.

Assessment of obesity parameters, CPX, and echocardiography. Obesity was defined on the basis of a body mass index (BMI) of ≥ 30 kg/m². Levels of BNP were compared in the obese and nonobese (BMI < 30 kg/m²) patients with respect to NYHA functional class and lean body weight-adjusted peak aerobic oxygen consumption (VO₂). Cardiopulmonary stress testing was accomplished using a ramping treadmill protocol, and breath-to-breath on-line gas analysis was performed using a MedGraphics CPXID metabolic cart (St. Paul, Minnesota). Incremental data, including minute ventilation, VO₂, and carbon dioxide production, were collected, and maximal VO₂, anaerobic threshold, and respiratory exchange ratio were calculated. Oxygen consumption was corrected for body fat and was reported as lean body mass-adjusted VO₂, as we reported previously (11). Echocardiography was performed in all patients and interpreted by investigators blinded to the clinical data and BNP data. Renal function was evaluated by using serum creatinine measurements (mg/dl) and by the calculated glomerular filtration rate.

Cytokine substudy. In a subset of 36 patients with NYHA class III heart failure, we measured plasma levels of tumor necrosis factor- α , interleukin-6, and soluble intercellular adhesion molecule-1 by means of enzyme-linked immunoassay. These cytokines were determined in obese and nonobese patients who were matched with respect to the

clinical severity of heart failure, left ventricular ejection fraction (LVEF), peak exercise VO₂, and medications used. **Outcomes analysis.** We also evaluated the combined end points of emergency department visits or hospitalizations for CHF or death in obese heart failure patients compared with nonobese subjects at 12 months after study entry.

Statistical analysis. Normally distributed data are reported as the mean value \pm SD. Categorical variables were compared using the likelihood ratio chi-square test. With continuous variables, group mean values were compared using the unpaired Student *t* test, as long as the variables were normally distributed within each group and the variation of scores in the two groups were not reliably different. The normality assumption was evaluated by examining the distribution of data (via histograms). If the data distribution did not follow the normality assumption, the Wilcoxon rank-sum test was utilized. Further multivariate analyses were performed to evaluate the independent relationship of BMI and BNP levels in concert with demographic variables (age, race, and gender), structural cardiac functional indexes (LVEF and LV end-diastolic diameter), severity of heart failure (NYHA class, lean peak VO₂), and renal function. Cox proportional hazard regression analysis was used to determine the independent predictors of event-free survival and included BMI, age, gender, ischemic versus nonischemic cardiomyopathy, functional classification, LVEF, renal function, BNP levels, and peak VO₂. All analyses were performed using StatView version 4.5 (Abacus Concepts Inc., Berkeley, California), and statistical significance was set at $p < 0.05$.

RESULTS

Patients. The study included 318 consecutive patients (age 57 ± 14 years; 57% men; 53% white) with CHF (LVEF $31 \pm 17\%$). All patients received maximal treatment using conventional therapy. Thus, 89% received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and 71% received beta-blockers. All received diuretics to "dry" weight. The total population's BMI was 29.4 ± 6.6 kg/m²; 24% were lean (BMI < 25 kg/m²), 31% overweight (BMI ≥ 25 – 29.9 kg/m²), and 45% obese (BMI ≥ 30 kg/m²). Obese patients with CHF were younger, more often African American, and more likely to have a history of antecedent hypertension, but less likely to have coronary artery disease and with only a trend toward diabetes mellitus (Table 1).

Comparison of BNP levels in obese and nonobese patients. Levels of BNP were significantly lower in obese than in nonobese subjects (205 ± 22 and 335 ± 39 pg/ml, respectively; $p = 0.0007$). These differences persisted even when the patients were regrouped into lean (BNP 366 ± 47 pg/ml), overweight (BNP 309 ± 34 pg/ml), or obese (BNP 205 ± 22 pg/ml, $p < 0.01$ for trend). However, there was no significance between the lean and overweight groups ($p = 0.3$), although the BNP level in overweight versus obese subjects was

Table 1. Baseline Characteristics

	Nonobese (n = 175)	Obese (n = 143)	p Value
Age (yrs)	60 ± 13	56 ± 13	0.04
Male gender (%)	59	53	0.3
Caucasian (%)	57	43	0.02
History of hypertension (%)	69	86	0.004
Coronary artery disease (%)	67	55	0.04
Diabetes mellitus (%)	32	41	0.07
LVEF (%)	30 ± 17	32 ± 17	0.1
LVEDD (mm)	5.6 ± 1.1	5.7 ± 1.0	0.3
NYHA class (%)			0.9
I/II	67	70	
III/IV	33	30	
SBP (mm Hg)	126 ± 23	127 ± 20	0.7
DBP (mm Hg)	69 ± 15	69 ± 14	0.8
Hemoglobin (gm/dl)	13.1 ± 1.8	13.1 ± 1.7	0.9
Hematocrit (%)	39.8 ± 4.7	39.8 ± 4.9	0.9
Blood urea nitrogen (mg/dl)	22 ± 13	24 ± 14	0.2
Serum creatinine (mg/dl)	1.3 ± 0.5	1.3 ± 0.5	0.5
GFR (ml/min)	71 ± 18	68 ± 14	0.4
VO ₂ lean (ml/kg/min)	22 ± 7	24 ± 5	0.2
ACE inhibitor or ARB (%)	90	91	0.8
Beta-blocker (%)	76	80	0.1
Diuretics (%)	89	90	0.8

Data are presented as the mean value ± SD or percentage of subjects.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; DBP = diastolic blood pressure; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; NYHA = New York Heart Association; SBP = systolic blood pressure; VO₂ lean = peak aerobic capacity adjusted for lean body weight.

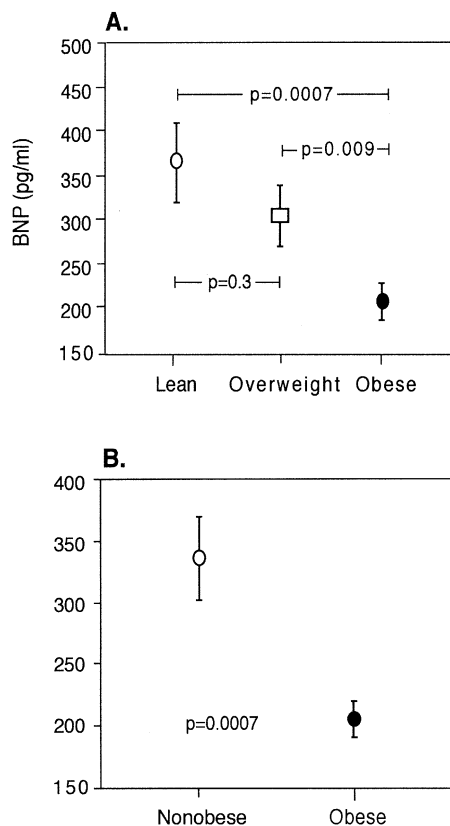


Figure 1. (A) Obese patients have lower circulating levels of B-type natriuretic peptide (BNP) compared with both lean and overweight patients with heart failure. (B) Difference in circulating levels of BNP in obese and nonobese patients (lean and overweight).

significantly less ($p = 0.009$). Thus, the group of overweight subjects was similar to the lean group with regard to BNP levels (Figs. 1A and B), but the differences in BNP levels between the obese and nonobese groups persisted even though they had a similar functional class. Thus, the LVEF, VO₂ corrected for lean body mass, serum creatinine, and glomerular filtration rate were similar between the two groups. To further evaluate the influence of age and its possible interaction with BNP levels in the context of obesity, we divided the cohort into the elderly (≥ 65 years old) and nonelderly (< 65 years old) and found that the relationship of obesity and decreased BNP levels persisted. Thus, the elderly obese patients had 28% lower BNP levels compared with elderly nonobese patients (BNP 290 ± 50 vs. 405 ± 48 pg/ml, $p = 0.03$). Similarly, the younger (< 65 years old) obese patients demonstrated 40% lower BNP levels compared with younger nonobese patients (175 ± 24 vs. 294 ± 35 pg/ml, $p = 0.006$). No significant interaction of diabetes mellitus as a determinant of BNP levels in the obese and nonobese subjects was noted. Regression analysis of BNP levels and BMI as a continuous variable revealed a weak but significantly inverse relationship between the two variables ($r = -0.36$, $p = 0.002$) (Fig. 2).

Multivariable predictors of BNP levels. Multivariate regression analysis identified BMI as an independent negative correlate of BNP levels ($t = -3.428$, $p = 0.0007$). Other independent correlates included age ($t = 3.001$, $p = 0.0003$), female gender ($t = 2.584$, $p = 0.01$), serum creatinine concentration ($t = 3.677$, $p = 0.0003$), NYHA class ($t = 4.731$, $p = 0.0001$), and LVEF ($t = -3.430$, $p =$

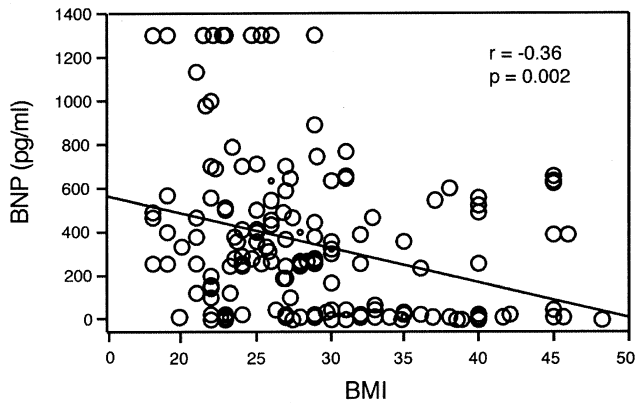


Figure 2. This figure depicts the raw data demonstrating a significant inverse correlation between circulating B-type natriuretic peptide (BNP) levels and body mass index (BMI).

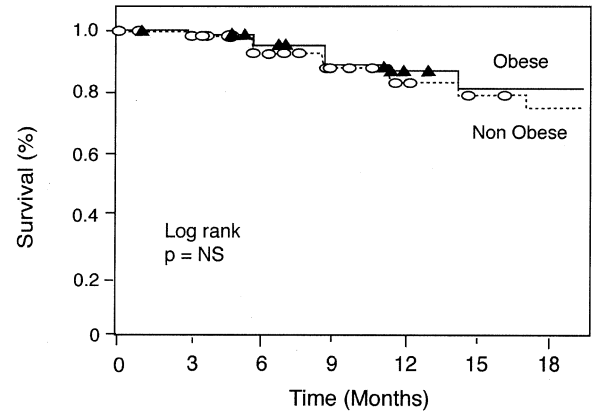


Figure 3. No difference in emergency department visits, heart failure hospitalization, or death between obese (triangles) and nonobese (circles) patients at 12-month follow-up was noted in the obese and nonobese patients with heart failure.

0.0007). In particular, we did not find any significant independent influence of diabetes mellitus on BNP levels.

Cytokine substudy findings. Although BNP levels were significantly lower in the obese ($n = 16$, 305 ± 124 pg/ml) versus nonobese ($n = 20$, 510 ± 141 pg/ml, $p = 0.01$ by Wilcoxon rank-sum test) comparison, there were no differences ($p = \text{NS}$ by Wilcoxon rank-sum test) in the three cytokines between these subgroups (Table 2). These findings suggest that the differences in BNP levels in obese patients were not related to differences in circulating levels of pro-inflammatory cytokines.

Outcomes. There were no significant differences in the time to first event (emergency department visit or hospitalization for CHF or death) between the obese and nonobese patients (Fig. 3). Moreover, the event rate for the entire cohort at one year was 27%, and this was not different between the obese (25%) and nonobese (29%) patients. In a Cox proportional hazards model stratified by obese and nonobese patients and including age (95% confidence interval [CI] 0.97 to 1.02), female gender (95% CI 0.68 to 2.8), LVEF (95% CI 0.97 to 1.01), serum creatinine (95% CI 0.73 to 1.7), and BNP level (95% CI 0.99 to 1.01) as covariates, there were no significant interactions noted. Only a higher NYHA class predicted a worse survival (CI 1.17 to 2.9, $p = 0.02$).

DISCUSSION

This study demonstrates that obesity is an important and independent determinant of peripheral BNP expression in patients with CHF. The implications of these findings not only extend to the usefulness of BNP as a diagnostic test in obese patients with heart failure, but also provide important insight into certain potential underlying pathophysiologic mechanisms that relate to the development of heart failure in obese patients. Thus, patients with obesity, even before development of heart failure, have an expanded intravascular (plasma) volume associated with an increased cardiopulmonary volume (6). Several recent studies have shown that natriuretic peptide levels are reduced in the obese state, partly related to altered clearance receptors and peptide degradation (9,10). These lines of evidence, coupled with our findings, provide endorsement for the presence of a reduced natriuretic response in the state of obesity. The suggestion that there may be increased clearance of BNP by adipose tissue raises the interesting possibility that there may be early loss of natriuretic-mediated vasodilation, lesser antagonism of the rennin-angiotensin system, or loss of natriuretic ability in obese patients.

Several investigations have alluded to obesity as a major risk factor for the development of heart failure (5-8),

Table 2. Cytokine Substudy

	Obese (n = 16)	Nonobese (n = 20)	p Value
BNP (pg/ml)	305 ± 124	510 ± 141	0.01
Tumor necrosis factor-alpha (pg/ml)	3.6 ± 4.2	3.5 ± 1.5	0.46
Interleukin-6 (pg/ml)	8.9 ± 6.7	8.6 ± 5.3	0.89
Soluble intercellular adhesion molecule-1 (ng/ml)	264 ± 75	292 ± 131	0.64

Data are presented as the mean value ± SD.
 BNP = B-type natriuretic peptide.

regardless of gender (8). Why the heart fails as a result of obesity continues to be a matter of intense investigative scrutiny. Several lines of evidence have pointed to hemodynamic overload, lipoapoptosis, impaired fatty acid oxidation, or the concerted effects of diffuse vascular damage, which are present early in childhood (12-15). Obesity is associated with an increased prevalence of most cardiovascular risk factors, including systemic hypertension, diabetes mellitus, hyperlipidemia, and LV hypertrophy (16). Moreover, because of coexistent volume overload with obesity and pressure overload with frequent hypertension, eccentric and concentric LV hypertrophy is expected (6). Our study supports this notion, as obese heart failure patients were younger and had a more prevalent history of hypertension and perhaps diabetes mellitus. Nevertheless, the precise mechanisms linking obesity to heart failure remain unresolved.

As already suggested, the natriuretic peptide system and adiposity are closely linked. Lipolysis is mediated by catecholamines (stimulation of lipolysis) and insulin (inhibition of lipolysis) (17). More recently, natriuretic peptides have been shown to be important stimuli for lipolysis in humans and similar in potency to catecholamines (18). Furthermore, since adipose cells express the natriuretic clearance receptor (19), in obese patients, a state of reduced natriuretic peptide concentration could occur, explaining the increased sodium retention and volume expansion characteristic of obesity-related hypertension (6). Fasting and weight loss are known to decrease expression of adipose cellular natriuretic peptide clearance receptors (20). Conversely, obesity is common after menopause, and it has been suggested that the decreased availability of circulating natriuretic peptides due to increased expression of the natriuretic clearance receptor could explain, at least in part, the increase in cardiovascular disease after menopause (21). Our study lends credence to these potential mechanisms and suggests that one possible explanation for the earlier expression of heart failure in the presence of obesity could be related to reduced circulating natriuretic peptides.

Thus, a paradox has emerged in the obese patient. On one hand, heart failure is increased in obese patients, but alternatively, a survival advantage in heart failure has been reported (22-24). Several lines of evidence have been suggested for diminished activation of natriuretic peptides, enhanced protection against endotoxin/inflammatory cytokines, and increased nutritional and metabolic reserve. All of these possibilities may explain the observation of better survival in obese patients with heart failure (25-28). As noted in our study, event-free survival was not different in obese and nonobese heart failure patients. Other studies have demonstrated this apparent obesity paradox by including patients with severe heart failure and cardiac cachexia. In the current study, no differences in the circulating pro-inflammatory cytokines were found, and the severity of heart failure (as evaluated by lean body weight-adjusted VO_2) was similar in obese and nonobese patients. These

observations suggest that the lower levels of natriuretic peptides in obesity did not confer a more favorable prognosis. This finding lends further credence to the concept that a state of reduced BNP level exists in obese patients with heart failure.

Conclusions. Obesity is associated with significantly lower peripheral expression of natriuretic peptides in heart failure. Our investigation indicates that a state of reduced natriuretic peptide level exists in the obese individual with heart failure.

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