Relationship Between Obesity and B-Type Natriuretic Peptide Levels

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**Background:** The relationships among B-type natriuretic peptide (BNP) levels, body mass index (BMI), and congestive heart failure (CHF) as an emergency diagnosis are unknown.

**Methods:** Of 1586 participants in the Breathing Not Properly Multinational Study who had acute dyspnea, 1369 (86.3%) had BNP values and self-reported height and weight. Two independent cardiologists masked to the BNP results adjudicated the final diagnosis.

**Results:** Congestive heart failure was found in 46% of participants. Individuals with higher BMIs were younger and had more frequent edema on examination but were equally as likely to have CHF vs noncardiac sources of dyspnea. A nearly 3-fold difference was seen in mean±SD BNP values at the low and high extremes of the BMI groupings (516.7±505.9 vs 176.3±270.5 pg/mL, respectively; *P* < .001). The correlations between BMI and log BNP among those with and without CHF were *r* = −0.34 and *r* = −0.21, respectively (*P* < .001 for both). Multivariate analysis for the outcome of log BNP among a small subset with CHF (n = 62) found that Framingham score (*P* = .002), estimated glomerular filtration rate (*P* = .007), female sex (*P* = .03), New York Heart Association functional class (*P* = .09), and third heart sound (*P* = .08) were independent predictors. However, BMI was not found to be independently related to log BNP (*P* = .59).

**Conclusions:** In patients with and without CHF, BNP levels are inversely related to BMI. When considering demographics, severity of disease, and renal function, BMI is not independently related to BNP levels in a small subgroup when detailed information about CHF severity is known.

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The prevalence of obesity has increased dramatically worldwide during the past 3 decades. Approximately 65% of Americans are overweight or obese, and the prevalence of morbid obesity (body mass index [BMI] calculated as weight in kilograms divided by the square of height in meters) ≥40) has more than doubled in the past decade. Similarly, there is an epidemic of congestive heart failure (CHF), with 5 million individuals with CHF in the United States and 500,000 new cases diagnosed each year. Clinical encounters in obese patients with dyspnea are becoming commonplace. Furthermore, obesity has been independently associated with incident CHF.

B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to pressure overload. Levels of BNP are reliably elevated in patients with CHF, and they correlate with New York Heart Association functional classifications and prognosis. However, age and sex also affect BNP levels. We sought to characterize the relationships among BMI, BNP levels, and patients evaluated in the emergency department (ED) for possible CHF.

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**Methods**

**Patient Population**

The Breathing Not Properly Multinational Study was an international 7-center prospective trial that evaluated the utility of BNP measurements for the diagnosis of CHF in the ED. The study design and results have been published elsewhere. The study was conducted between April 1, 1999, and December 31, 2000, and was approved by the institutional review board of each participating medical center. Briefly, 1666 patients older than 18 years presenting to the ED with the primary complaint of dyspnea were screened. Eighty patients met the exclusion criteria: advanced renal failure (dialysis or a glomerular filtration rate < 15 mL/min per 1.73 m²), acute coronary syndrome, or trauma. A total of 217 patients had missing BMI data, leaving 1369 patients for the final analysis.
MEASUREMENT OF BNP

During the initial evaluation in the ED, a 5-mL blood sample was collected in a tube containing potassium EDTA. B-type natriuretic peptide concentration was measured using a fluorescence immunoassay (Triage BNP Test; Biosite Inc, San Diego, Calif). The precision, analytical sensitivity, and stability characteristics of the assay have been described previously. Univariate results of BNP measurement were masked to clinicians.

REFERENCE STANDARD FOR HEART FAILURE

Approxiately 30 days after the initial ED visit, the ED record, inpatient record, discharge summary, chest radiography report, electrocardiogram at presentation, and all clinical test results were reviewed by 2 independent cardiologists at each study center. If agreement was achieved after reviewing all information, each case was categorized as (1) dyspnea due to CHF, (2) dyspnea with a noncardiac cause, or (3) history of CHF but dyspnea with a noncardiac cause. If agreement was not achieved, the end points committee adjudicated the cases. For binary analyses of CHF vs no CHF, groups 2 and 3 were combined. As previously reported in the overall study, cardiologists at each study center evaluated all clinical data, including echocardiograms with reported ejection fractions, in 689 cases (44.8%). There was initial agreement between the 2 cardiologists in 1374 cases (89.3%). The remaining 164 cases were adjudicated locally by the 2 cardiologists, with additional data from the treating physicians and review by the end points committee if disagreement remained. The diagnosis of CHF (n=722) was supported by positive NHANES (National Health and Nutrition Examination Survey) and Framingham scores in 599 (83.0%) and 621 (86.0%) cases, respectively. The cardiologists reported support for the diagnosis of CHF by chest radiography in 587 cases (86.0%) and echocardiography, nuclear ventriculography in 34 (4.7%), and cardiac catheterization in 55 (7.6%). In addition, the cardiologists reported that 490 patients with CHF (67.9%) had an expected response to CHF therapy. Conversely, 684 (91.4%) of the 748 patients without CHF had cumulative evidence from chest radiography, echocardiography, or ventriculography to suggest that CHF was not the cause of dyspnea. Overall, 36.5% of individuals with echocardiograms had preserved systolic function (ejection fraction > .45%).

REPORTING OF BODY WEIGHT AND SIZE

Body height and weight were by self-report and by actual measurement, with variations by study center. Given the inherent differences in these measures and the confounding issue of edema and body weight accounted for by excess body fluid, a variety of measures were used: (1) body weight by self-report or actual weight (original database value), (2) estimated lean body weight from height using the following formulas: men—50 kg+2.3 kg×[height (in inches)−60]; women—45.3 kg+2.3 kg×[height (in inches)−60]; (3) estimated lean body weight from height and weight as recorded in the database using the following formulas: men—[1.10 × weight (in kilograms)]−128/weight2/100×height [in meters]2; women—[1.07 × weight (in kilograms)]−148/weight2/100×height [in meters]2; and (4) calculated body surface area (BSA) using the following formula: BSA (m2)=weight (in kilograms)0.331035×height (in centimeters)0.2236×0.023530 (formula of Ghan and George). The following Pearson correlations were considered: database body weight×lean body weight from height, 0.35 (P < .001); database body weight×lean body weight from height and weight, 0.50 (P < .001); BMI×lean body weight from height, −0.08 (P = .002); and BMI×lean body weight from height and weight, 0.13 (P < .001). Accordingly, a lean body weight variable was constructed from the lean body weight estimated from height and weight (in kilograms) divided by the square of the height in meters and was considered as a secondary variable for analysis along with conventionally calculated BMI from the database height and weight.

STATISTICAL ANALYSIS

Univariate statistics were reported as mean±SD or counts, with proportions as appropriate. The χ2 test or 1-way analysis of variance was used to determine differences between groups. Because BNP levels were not normally distributed, the log BNP was used in correlations and regression models. The univariate relationships between measures of body size and log BNP were tested using the Pearson correlation. Multiple linear regression was used to analyze the strength of association between log BNP and BMI after adjusting for age, sex, history of CHF, New York Heart Association classification, and echocardiographic and other baseline factors not significant in the univariate analysis.

RESULTS

A total of 1369 participants had valid information for all direct and calculated variables. Patients were aged 63.4±16.3 years; 54.8% were male; 45.1% were white and 49.7% were African American, and 46.2% had a final diagnosis of CHF and 53.8% had a final diagnosis of noncardiac dyspnea, primarily asthma or chronic obstructive pulmonary disease. The clinical characteristics are given in Table 1 by BMI classification: underweight (< 20.0), normal (20.0-24.9), overweight (25.0-29.9), obese class I (30.0-34.9), obese class II (35.0-39.9), and obese class III (≥ 40.0). As seen in Table 1, patients who were overweight or obese were younger and had more frequent edema on examination but were equally as likely to have CHF vs noncardiac sources of dyspnea. The data in Table 1 also demonstrate that body weight as recorded in the database, not height, differed across the BMI categories and hence was the principal determinant of BMI. The mean and median BNP levels according to BMI for the study population are also given in Table 1. A nearly 3-fold difference was seen in mean BNP values at the extremes of the BMI groupings (516.7±505.9 vs 176.3±270.5 pg/mL for those with BMI < 20.0 vs ≥ 40.0; P < .001). Among those with CHF and recorded ejection fractions in the database (n = 663), there was no trend for increasing rates of diastolic heart failure (ejection fraction > .45%) according to BMI category (ejection fractions of 25.0%, 19.9%, 25.1%, 23.1%, 26.3%, and 32.1% for patients with a BMI < 20.0, 20.0-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, and ≥ 40.0, respectively; P = .15). Figures 1 and 2 show scatterplots of log BNP and BMI in patients with and without CHF, respectively. Note that in patients with CHF, values are truncated owing to the upper measurable limit of BNP in the study of 1300 pg/mL. As shown, most BNP values at or above the normal range occurred in patients in the lower BMI categories. However, in individuals without CHF (Figure 2), BNP values are truncated at the lower range and extend from a BMI of 20 through 50. Table 2 gives the Pearson product moment correlations between the measures
weight and log BNP for participants with and without CHF. The relationships between log BNP and measures of body size were stronger in individuals with CHF than in those without CHF. Figure 3 displays the frequency of markedly elevated (>1000 pg/mL) BNP levels by BMI category in participants with CHF, indicating a strong trend for those with lower body weight to have higher BNP values. Conversely, Figure 4 shows the frequency of low (<50 pg/mL) BNP values in participants without CHF according to BMI category. Except for participants with the
lowest BMI (<20.0), more than 50% of each BMI category had BNP values of less than 50 pg/mL, which are considered in the normal range for patients with normal left ventricular function. The linear trend for higher rates of BNP values less than 50 pg/mL persisted even when the lowest BMI group was excluded (P = .004). The area under the receiver operating characteristic curve for BNP in the diagnosis of CHF was high and similar at 0.90, 0.92, and 0.89 for those with a BMI of less than 20.0, 20.0 to 24.9, and 25 or greater, respectively.

Multivariate modeling was restricted to patients (n = 62) who had complete data on body measures, echocardiography, CHF severity, renal function, and other known predictors of BNP levels. The distributions of those included and excluded from the multivariate analysis were the same, with mean BMI values of 28.7 ± 7.3 and 28.7 ± 8.4, respectively (P = .39). In addition, there was no difference between the skewness of the populations (1.4 vs 1.5). The results of the multivariate model for participants with CHF are given in Table 3. Known determinants of BNP levels, including sex (higher for women), estimated glomerular filtration (calculated from age, sex, serum creatinine level, and race using the Modification of Diet in Renal Disease 4-variable equation), CHF severity (reflected by the Framingham score and New York Heart Association functional classification), and the presence of a third heart sound, were independent predictors of log BNP. When adjusting for these factors, BMI was not an independent predictor. When the regressions were repeated with lean BMI, again, no independent association with log BNP was found. The model had an overall F statistic of 3.86 (P < .001).

This study demonstrated a modest univariate correlation with log BNP and BMI in individuals with acute dyspnea (r = −0.21 to −0.34). The results of our analysis suggest that this relationship is driven by the observation that patients with CHF and a smaller body size had greater frequencies of markedly elevated BNP values. This finding is in keeping with the observation that patients with CHF and a smaller body size have a greater degree of cardiac cachexia and higher mortality rates.18-21 Conversely, in individuals without CHF, lower levels of BNP tended to occur in participants with larger BMI values. Our multivariate analysis, in a very small subset, found that there was no independent relationship between BMI and BNP when we accounted for the known factors affecting BNP, such as sex; age-derived variables, including renal function; and CHF severity. There was an approximate 1:1 ratio of African Americans to whites in the BMI categories, but this ratio increased to almost 2:1 in the highest BMI categories. However, according to the multivariate analysis, African Americans to whites in the BMI categories, but this ratio increased to almost 2:1 in the highest BMI categories. However, according to the multivariate analysis, African American race was not statistically significantly related to the measured BNP value. Our findings suggest that much of the inverse relationship between BMI and BNP can be explained by confounding, particularly by age in individuals without CHF and by the severity of disease in those

### Table 3. Independent Predictors of Log BNP in 62 Patients With CHF With Full Information About CHF Severity and Echocardiographic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized β Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham score</td>
<td>0.477</td>
<td>.002</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate</td>
<td>−0.323</td>
<td>.007</td>
</tr>
<tr>
<td>Female sex</td>
<td>−0.289</td>
<td>.03</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>0.229</td>
<td>.09</td>
</tr>
<tr>
<td>Third heart sound</td>
<td>0.207</td>
<td>.08</td>
</tr>
<tr>
<td>NHANES score</td>
<td>−0.136</td>
<td>.27</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>0.199</td>
<td>.14</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td>−0.179</td>
<td>.13</td>
</tr>
<tr>
<td>History of CHF</td>
<td>−0.081</td>
<td>.47</td>
</tr>
<tr>
<td>LV end-systolic dimension</td>
<td>0.075</td>
<td>.69</td>
</tr>
<tr>
<td>Age</td>
<td>0.078</td>
<td>.56</td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.067</td>
<td>.59</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>−0.010</td>
<td>.95</td>
</tr>
</tbody>
</table>

Abbreviations: BNP, B-type natriuretic peptide; CHF, congestive heart failure; LV, left ventricular; NHANES, National Health and Nutrition Examination Survey; NYHA, New York Heart Association.
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with CHF. These observations are in agreement with those from previous studies14,22 that demonstrated that BNP values are lower in patients who are younger and less ill.

The reason for the relationship between lower BMI and elevated BNP levels in patients with CHF is uncertain, but several possibilities exist. Cardiac cachexia has been a well–described condition associated with advanced CHF and, consistent with marked elevations of BNP concentration, portends a poor prognosis.23,24 Hence, the finding of very high levels of BNP in patients with CHF and low body weight can simply be explained by severity of disease. Another distinct possibility is misclassification of the cause of dyspnea in individuals determined to have CHF. Physical examination, chest radiography, and echocardiographic interpretation are particularly challenging in obese individuals, who are at higher risk of having CHF than nonobese individuals.25–30 Obese patients thought to have CHF with lower or normal BNP levels may not have had CHF as the actual cause of their dyspnea. This could in part explain why in other studies obese patients with CHF seem to have a better prognosis (the “obesity paradox”).19 The diagnosis of diastolic CHF may be particularly susceptible to misdiagnosis in patients with obesity.31 However, we did not find higher rates of preserved systolic function in the higher BMI categories in patients with CHF. Finally, BNP level is, to a great extent, degraded by clearance receptors and neutral endopeptidase mostly located in the kidney but also found in the lungs, brain, heart, and peripheral vasculature.32–39 Adipose tissue may afford another source of available clearance receptors and neutral endopeptidase, leading to more rapid degradation of BNP. In addition, natriuretic peptides have recently been found35,36 to be lipolytic in adipose tissue; hence, higher BNP levels may have potentially facilitated weight loss and the lower body weights we observed in individuals with high BNP levels. Although speculative, this may in part explain the weak correlations between BMI and BNP levels in individuals without CHF.

There are several limitations to our study. First, self–reported height and weight were used to calculate BMI, which may have led to inaccuracies. However, we believe that the use of calculated lean BMI would have been even more problematic because it may not be accurate in the setting of cardiac cachexia. Second, there were many patients without echocardiographic data who, therefore, could not be included in the multivariate analysis (which included 62 of 1369). Finally, this study has many of the same limitations related to any study attempting to use a clinical diagnosis as a gold standard for a syndrome. The reviewing cardiologists had all possible medical records to review, but we acknowledge that misclassification of the final diagnosis was possible but was likely to be nonrandom and impossible to quantify in the absence of a more objective reference standard.

In conclusion, high levels of BNP in patients with low body weights and, likely, advanced CHF accounted for the inverse relationship between BNP levels and BMI. There does not seem to be an independent relationship between measures of body weight or size and BNP when all other factors are taken into account. Clinicians should be wary of the univariate relationship between BMI and BNP level that we have demonstrated in the present study.

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